11th International Symposium of GASTROENTEROLOGY

Abstracts

12–14 May 2016, Saint Petersburg, Russia

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11th INTERNATIONAL SYMPOSIUM OF GASTROENTEROLOGY

Saint Petersburg, Russia, 12–14 May 2016

Topics:

NAFLD and comorbidity
Progress in therapeutic endoscopy
Inflammatory bowel disease
Diagnostic and therapeutic approaches in GERD
Hepatology
Colorectal malignancy

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President of Czech Society of Gastroenterology

Professor Vladimir T. IVASHKIN
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CONTENTS

11th International Symposium of GASTROENTEROLOGY

ORAL PRESENTATION ABSTRACTS

METABOLIC SYNDROME – OBESITY AS A RISK FACTOR FOR GI-DISEASE DEVELOPMENT

Petr DITE

Department of Gastroenterology, Metabolism and Nutrition, Clinic of Internal Medicine, University Hospital and Faculty of Medicine Ostrava; Czech Republic

Metabolic syndrome, whose harmonized definition has been internationally adopted, including in the Czech Republic, is a set of 5 phenomena which have not been selected randomly. The presence of three of these is positive for the diagnosis of metabolic syndrome. Metabolic syndrome is most frequently associated with diseases of the cardiovascular system/cardiometabolic syndrome. Recently, however, knowledge concerning the possible role of metabolic syndrome has been rapidly increasing, especially if obesity and dyslipidemia are present among its components.

Gastro-oesophageal reflux is a condition induced by the presence of obesity. An important role is also played by insulin resistance as one of the phenomena of metabolic syndrome. Similarly, attention is drawn to a possible relationship between obesity and Barrett's oesophagus.

Non-alcoholic fatty liver in persons with metabolic syndrome is very common. The disease's progression to liver fibrosis or even cirrhosis has been terminally described. Similarly, cholelithiasis is one of the diseases in patients with metabolic syndrome.

Recently, attention has been paid to findings of steatopancreatitis in obese persons, or persons with dyslipidemia. The clinical meaning is not clear; some patients have signs of exocrine pancreatic insufficiency. However, the relationship with the beta cells of the pancreas and insulin secretion is probably more significant.

Metabolic syndrome has been described in relation to colorectal cancer, hepatocellular carcinoma and pancreatic cancer. Therefore, it is worth considering whether influencing the parameters of metabolic syndrome, including lifestyle changes, will not be one of the phenomena contributing significantly to the reduction of the development of some of the aforementioned tumours.

Dite P. Metabolic syndrome – Obesity as a risk factor for GI-disease development. In: *11th International Symposium of Gastroenterology, Saint Petersburg, Russia, 12–14 May 2016*. [online].
Available from URL: http://www.promedcs.eu/sites/default/files/abstractbook_2016.pdf

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METABOLIC SYNDROME – OBESITY AS A RISK FACTOR FOR GI-DISEASE DEVELOPMENT

Petr DITE

INTERNAL CLINIC – DEPT OF GASTROENTEROLOGY, UNIV. HOSPITAL OSTRAVA

CZECH REPUBLIC

METABOLIC SYNDROM

- is a constellation of cardiovascular risk factors including abdominal obesity, impaired glucose control, hypertension, dyslipidemia.

Grundy, *et al.* Circulation 2005

METABOLIC SYNDROM

- is a risk factor for GIT diseases, liver and pancreato-biliary diseases.
- and MetS components play important role in cancerogenesis.

HARMONIZING THE MET. SYNDROME CRITERIA FOR CLINICAL DIAGNOSIS

ELEVATED WAIST CIRCUMFERENCES	**MEN > 102 CM**	**WOMEN > +88 CM**
ELEVATED TRIGLYCERIDAEMIA		**> 1.7 MMOL/L**
REDUCED HDL-CHOLESTEROL	**< 1.0 MMOL/L (MALES)**	**< 1.3 MMOL/L (FEMALES)**
ELEVATED BLOOD PRESSURE	**SYSTOLIC > 130**	**DIASTOLIC > 85 mmHg**
ELEVATED FASTING GLUCOSE	**> 100 MG/Dl**	

For diagnosis – 3 positive components

Circulation 2009; 120: 1640–1645

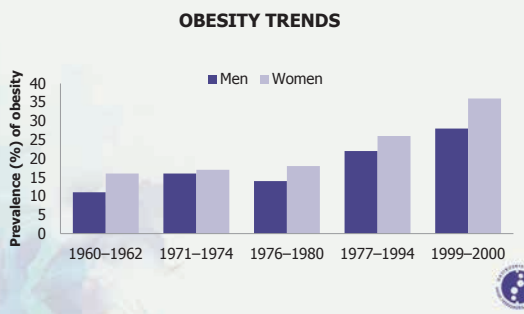
THE BODY MASS INDEX (BMI) – (QUETELET'S INDEX)

- WEIGHTS (kg) divided by HEIGHTS (m^2)
- WEIST CIRCUMFERENCE – for central obesity
- + BMI could be LESS VALID INDICATOR of obesity in OLD PERSONS – fat could be shift from peripheral to central site – CAVE in pts with VISCERAL/ABDOMINAL, FAT

STANDARDS DEFINING *HEALTHY* WEIGHT, *OVERWEIGHT* AND *OBESITY* ARE ACCORDING GLOBAL ACCEPTED CRITERIA ON *BODY MASS INDEX* (BMI)

BMI (kg/m²)	WHO CLASSIFICATION	POPULAR DESCRIPTION
< 18.5	UNDERWEIGHT	THIN
18.5–24.9	NORMAL RANGE	HEALTHY
24.9–29.9	OVERWEIGHT (grade 1)	OVERWEIGHT
30.0–39.9	OBESITY (OVERWEIGHT gr 2)	OBESITY
> 40	OBESITY (OVERWEIGHT gr 3)	MORBID OBESITY

TRENDS OF ADJUSTED PREVALENCE OF OBESITY IN ADULTS AGED 20–74 YEARS IN USA



PREVALENCE OF ADULT OBESITY IN SOME EUROPEAN COUNTRIES

	MEN > 30y		WOMEN > 30y	
	BMI 25–30	BMI > 30	BMI 25–30	BMI > 30
AUSTRIA	76.0	30.7	65.8	29.2
BULGARIA	54.7	22.1	63.3	28.3
CZECH REP.	73.0	26.8	66.5	30.9
FRANCE	56.3	11.3	42.7	9.6
GERMANY	75.4	28.8	66.4	28.7
HUNGARY	69.3	22.5	60.4	20.4
POLAND	65.4	18.8	62.6	26.9
U.K.	76.2	29.5	69.4	31.7
SLOVAKIA	61.5	14.9	67.1	29.0
RUSSIA	58.1	14.0	69.6	34.8
USA	79.3	42.3	77.0	48.6
TANZANIA	20.9	1.0	32.5	4.3

PREVALENCE OF METABOLIC SYNDROME IN CZECH POPULATION 1998–2009

	1998	2005	2009
MEN	38.3%	35.9%	37.6%
WOMEN	29.7%	26.9%	25.9%

Rosolova H., *et al.* 2012

MOST RISK FACTORS OF METABOLIC SYNDROME IN CZECH POPULATION

	MEN	WOMEN
1)	ARTERIAL HYPERTENSION	ARTERIAL HYPERTENSION
2)	HYPERTRIGLYCEREDEMIAS	WAIST CIRCUFERENCE

OBESITY			
PREVALENCE OF MetS IN	MEN AGE	< 50y	20.0%
	MEAN AGE	> 50y	32.0%
	WOMEN AGE	< 50y	9.0%
	MEAN AGE	> 50y	30.0%

MAIN PATHOPHYSIOLOGICAL MECHANISMS OF MetS DEVELOPMENT

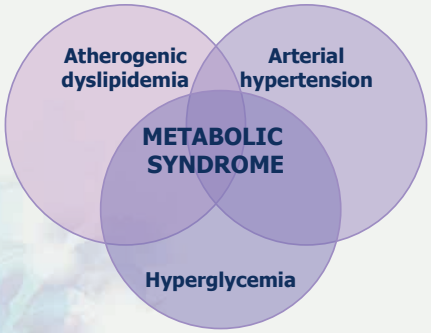
INSULIN RESISTENCE HYPERGLYCEMIA

CHRONIC INFLAMMATION

ENDOTHELIAL DYSFUNCTION

PROATHEROGENETIC STATUS

PATHOGENETIC DENOMINATORS



Alberti K.G.M.M., *et al.* Circulation 2009; 120: 1640–1645

METABOLIC SYNDROME AND GI TRACT

Esophagus:	**GERD, Barrett's esophagus**
Stomach:	**motility disorders?**
Gall bladder:	**stones**
Liver:	**fatty liver, fibrosis & cirrhosis**
Pancreas:	**↗ frequency & severity of acute inflammation**
Mlg. diseases:	**colorectal, biliary, hepatic, pancreatic**

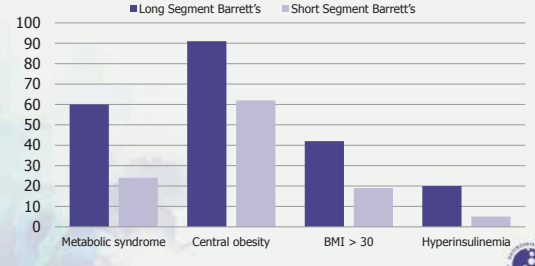
METABOLIC SYNDROME AND GERD

- **Mechanical factors**
  - Increased intragastric pressure
  - Increased risk for hiatal hernia development
  - Transient lower esophageal sphincter relaxation (through gastric distension)
- **Metabolic factors**
  - Increased levels of pro-inflammatory cytokines

Ierardi E., *et al.* World J Gastrointest Patophysiol 2010; 1(3): 91–96

BARRETT'S ESOPHAGUS

Prevalence of Central Adiposity, Metabolic Syndrome and a Proinflammatory State



Ryan A.M., *et al.* Ann Surg 2008; 247: 909–915

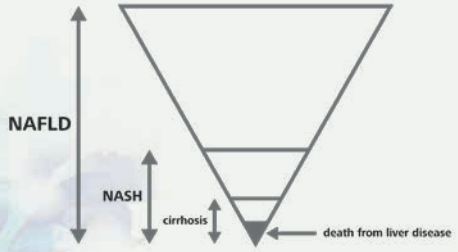
ESOPHAGEAL COX-2 EXPRESSION IS INCREASED IN BARRETT'S ESOPHAGUS, OBESITY AND SMOKING

- **CYCLOOXYGENASE-2** – a membrane bound glycoprotein that catalyzed the rate limiting-step in the production of prostaglandins from arachidonic acid
- **COX-2** – the role in the development GI-cancers, incl. esophageal cancer
- **SIGNIFICANT** association between elevated COX-2 level in mucosa and the presence Barrett's tissue
- association between COX-2 level, Barrett and smoking
- association between high COX-2 expression and waist-to-hip ratio

Ngyen T., *et al.* Dig Dis Sci 2015

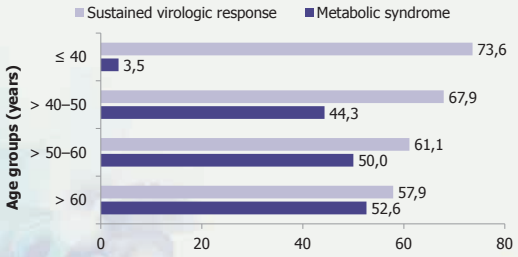
NAFLD

- Hepatic manifestation of metabolic syndrome



Neuschwander-Tetri B.A. Am J Med Sci 2005; 330(6): 326–225

METABOLIC SYNDROME AND RESPONSE TO HCV



Sustained response to peginterferon-α2a plus ribavirin treatment in different age groups of hepatitis C virus patients.

Aziz, *et al.*, 2014

STATISTICAL DIFFERENCE BETWEEN GROUPS IN TERMS OF MetS CRITERIA COUNT

Groups	MetS criteria count						χ^2	P
	0	1	2	3	4	5		
Crohn's disease	29% (n = 18)	30.6% (n = 19)	22.6% (n = 14)	12.9% (n = 8)	4.8% (n = 3)	0% (n = 0)	17.43	0.004
Ulcerative colitis	7.8% (n = 9)	40.9% (n = 47)	21.7% (n = 25)	20% (n = 23)	4.3% (n = 5)	5.2% (n = 6)		

Yorulmaz, *et al.*, 2011

DEMOGRAPHIC, CLINICAL AND LABORATORY CHARACTERISTICS OF PATIENTS WITH IBD

	Ulcerative colitis	Crohn's disease	*P* values
n	115	62	
Gender (female/male)	49/66	28/34	> 0.05
Age, mean ± SD (years)	43.93 ± 13.59	36.74 ± 13.88	> 0.05
Disease duration, mean ± SD (months)	50.18 ± 55.59	47.71 ± 70.16	> 0.05
Current smoker	22 (19.1%)	29 (46.8%)	< 0.001
Alcohol usage	16 (13.9%)	12 (19.4%)	> 0.05
BMI, mean ± SD (kg/m²)	26.27 ± 4.89	23.67 ± 5.18	< 0.01
Waist circumference (cm) – Female	97.37 ± 12.55	89.82 ± 15.97	< 0.05
Waist circumference (cm) – Male	97.53 ± 12.69	90.47 ± 10.74	< 0.01
SBP (mmHg)	122.43 ± 19.58	111.13 ± 20.96	< 0.001
DBP (mmHg)	78.39 ± 11.93	71.45 ± 12.78	< 0.001
FPG (mg/dl)	98.95 ± 32	91.87 ± 17.04	> 0.05
Triglycerides (mg/dl)	121.26 ± 57.29	121.15 ± 63.47	> 0.05
HDL-C (mg/dl) – Female	61.92 ± 12.84	56.04 ± 15.56	> 0.05
HDL-C (mg/dl) – Male	48.53 ± 14.48	51.12 ± 14.93	> 0.05
Insulin (μU/ml)	8.81 ± 5.30	7.34 ± 5.39	> 0.05
HOMA-IR	2.20 ± 1.57	1.69 ± 1.27	< 0.05

BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; FPG: Fasting plasma glucose; HOMA-IR: Homeostasis model assessment of insulin resistance

Yorulmaz, *et al.*, 2011

META-ANALYSES OBESITY OR BMI AS A PROGNOSTIC FACTOR FOR SEVERITY IN ACUTE PANCREATITIS

Reference year of publication (country of publication)	Definition of obesity	Definition of severity classification	Risk of severe acute pancreatitis	Outcome	Level of evidence
Chen, *et al.* 2012 (China)	BMI ≥ 25 kg/m² (Asian) BMI ≥ 30 kg/m² (Western)	Atlanta Criteria	RR: 2.20, 95% CI 1.82–2.66, p < 0.05	+	1a
Hong, *et al.* 2011 (Taiwan)	BMI > 30 kg/m²	Atlanta Criteria	RR: 1.82, 95% CI: 1.44–2.30	+	1a
Wang, *et al.* 2011 (China)	BMI ≥ 30 kg/m²	Atlanta Criteria	OR: 2.48, 95% CI 1.24–4.60	+	1a
Martinez, *et al.* 2006 (Spain)	BMI ≥ 30 kg/m²	Atlanta Criteria	OR: 2.9, 95% CI 1.8–4.6	+	1a
Martinez, *et al.* 2004 (Spain)	BMI ≥ 30 kg/m²	Atlanta Criteria	OR: 2.6, 94% CI 1.5–4.6	+	1a

BMI: Body Mass Index; RR: Relative risk; OR: Odds Ratio
Levels of evidence 1 adapted from Oxford Centre for Evidence – Based Medicine (2009)

NON-ALCOHOLIC STEATOPANCREATITIS

- **FIRST DESCRIPTION OF STEATOPANCREATITIS** – Ogilvie in 1933 in the group of obese patients in 17.1% steatosis of the gland was found versus 9.4% in control.

  Ogilvie, J. Pathol 1933; 37: 473–481
- **ENDOCRINE PART OF THE GLAND** – hypertrophy of islet of the langerhans.
- **OLSEN'S STUDY** – grading of pancreatic fat (1–4). Relationship between of the content fatty cells into the pancreas and age and between the fat in the gland and overweight – without the presence of diabetes mellitus.

RELATIONSHIP BETWEEN INSULIN AND PANCREATIC STEATOSIS

- Fat accumulation in pancreatic islets – decrease of insulin secretion – it's a explanation why insulin resistant people cannot encounter higher demands of insulin – developing DM type 2?

  Pezzillii R., Calcullin L. World J Diabetes, 2014
- **RESUME:** Toxic effect of long term pancreatic fat accumulation – beta-cel damage is present more than decade before diabetes is diagnosed.

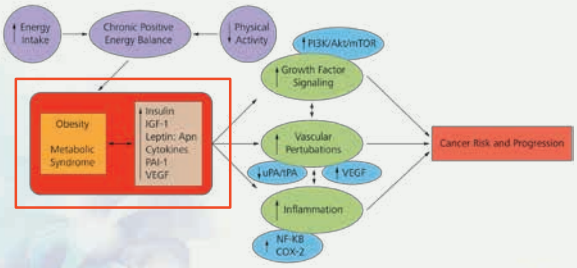
  Oakes N.D., *et al.*, Diabetes 1977

PANCREATIC STEATOSIS AND EXOCRINE PANCREATIC FUNCTION

- Only a case reports have reported the exocrine pancreatic insufficiency – according the grade od pancreatic tissue infiltration by fat.

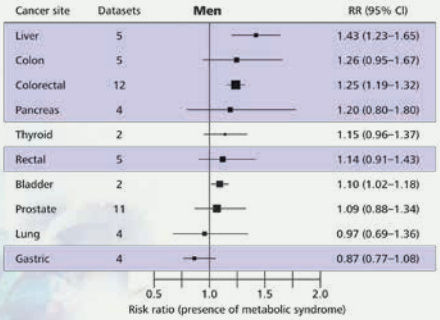
  Aubert, *et al.* J. Gastroent. Clin. Biol. 2007

MetS AND CANCER

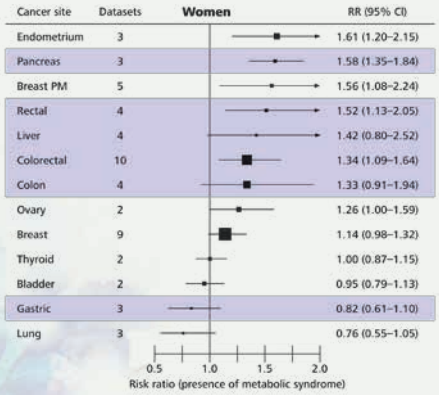


Hursting S.D., *et al.* Arterioscler Thromb Vasc Biol 2012; 32: 1766–1770

MetS AND RISK OF CANCER
A SYSTEMATIC REVIEW AND META-ANALYSIS



Esposito K., *et al.* Diabetes Care 2012; 35: 2402–2411



Esposito K., *et al.* Diabetes Care 2012; 35: 2402–2411

CONCLUSION

- **Metabolic syndrome** is a risk factor for diseases of GIT, liver and pancreato-biliary diseases
- **Metabolic syndrome** and mets components play important role in cancerogenesis
- Preventive and therapeutical strategy incl. the therapy of obesity is crutial!

CURRENT APPROACHES TO DIAGNOSIS AND TREATMENT OF NAFLD

Mark THURSZ

Imperial College, London; United Kingdom

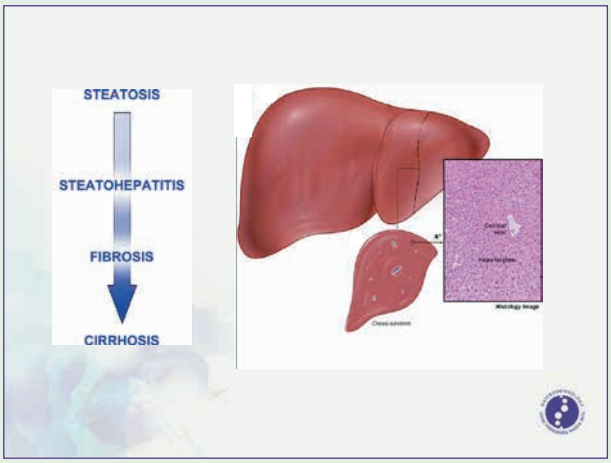
Globally there is an epidemic of obesity with increasing proportions of all populations having body mass indices greater than 30 kg/m^2. Whilst it is recognised that this epidemic has resulted in a high prevalence of diabetes and cardiovascular risk the hepatic consequences of obesity have not been fully appreciated. Non-alcoholic fatty liver disease (NAFLD) is the hepatic component of the metabolic syndrome and is frequently found in patients with obesity, hypertension, hyperlipidaemia and insulin resistance.

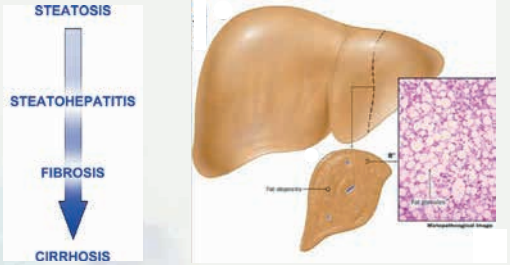
NAFLD represents a spectrum of histological severity from simple steatosis to non-alcoholic steatohepatitis (NASH), cirrhosis and hepatocellular carcinoma. Diagnosis of the disorder is usually straightforward even though there is no specific diagnostic test. The risk of disease progression is substantially higher in patients with NASH than those with simple steatosis making it important to classify patients carefully at the time of presentation. However, this can be difficult to achieve without liver histology.

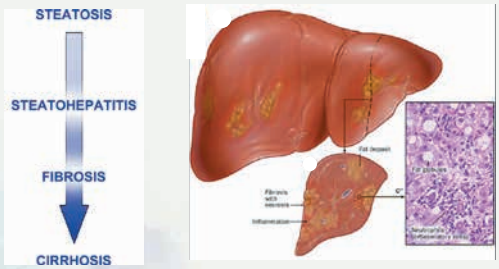
Primarily the management of this condition should focus on lifestyle modifications which result in weight loss. This can be challenging to achieve and in selected cases bariatric surgery may be required. Increasing exercise even in the absence of weight loss may be effective.

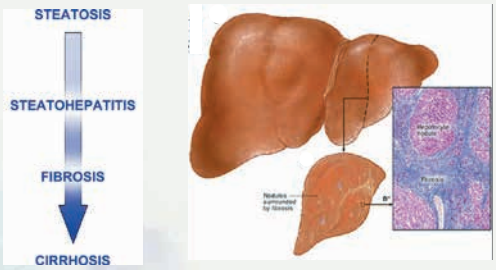
There are currently no specific treatment licensed for the management of NASH. Insulin sensitisers (metformin and pioglitazone) may be of benefit even in patients who do not have type II diabetes. High dose vitamin E has also been shown to be beneficial in clinical trials. Ursodeoxycholic acid may improve liver function tests and there is encouraging data from a recent phase II trial of the FXR agonist obeticholic acid.

Thursz M. Current approaches to diagnosis and treatment of NAFLD. In: *11th International Symposium of Gastroenterology, Saint Petersburg, Russia, 12–14 May 2016*. [online].
Available from URL: http://www.promedcs.eu/sites/default/files/abstractbook_2016.pdf





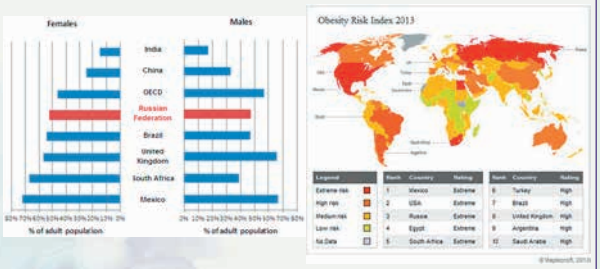




NON-ALCOHOLIC FATTY LIVER DISEASE

- UK adult obesity (BMI>30)
  - 1980: 6% [M], 8% [F].
  - 1997: 17% [M], 20% [F].
- By 2004, 23.6% of men and 23.8% of women were obese in England and Wales.

OBESITY, A GLOBAL PROBLEM

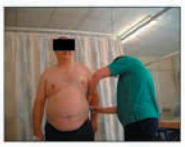


NAFLD: frequently occurs with Metabolic Syndrome:

a condition of ectopic fat accumulation, insulin resistance and cardiometabolic risk factors

Metabolic Syndrome Features 2009	
Waist	> 94/80 cm
BP	≥ 130/85
TG	≥ 1.7mmol/l
Glucose	≥ 5.6 mmol/l
HDL	< 1.0/1.3 mmol/l

↑ Triglyceride
↓ HDL Cholesterol
↑ BP



NAFLD
Central obesity

Glucose intolerance & type 2 diabetes

Vascular inflammation, a procoagulant phenotype & heart disease

Byrne C & Wild S eds, Metabolic syndrome Wiley-Blackwell 2011

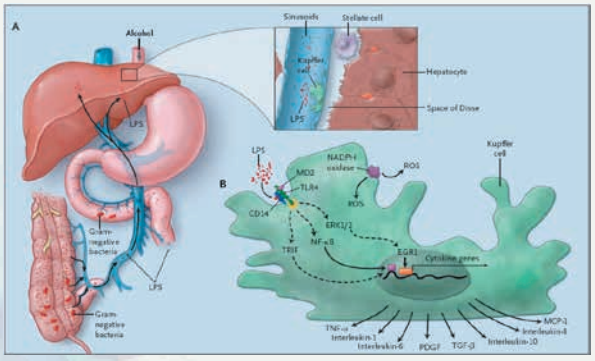
NAFLD ASSOCIATES WITH CVD

Independent of other CVD risk factors

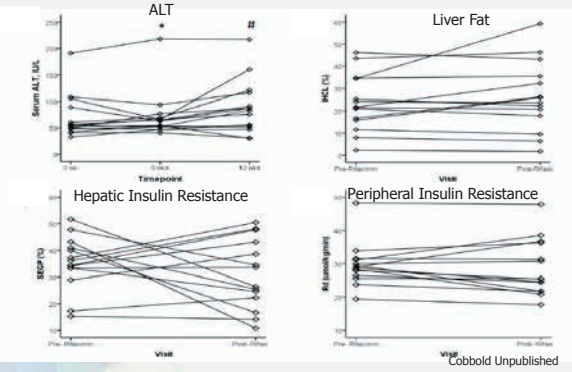
- Amongst diabetics NAFLD increases risk of
  - Coronary artery disease
  - Cerebrovascular disease
  - Peripheral vascular disease
- More severe coronary disease
- NASH increases risk more than steatosis
- Increased carotid intimal thickness
- Coronary artery calcification
- Impaired flow mediated vasodilation
- Increased arterial stiffness
- Carotid artery inflammation

Byrne. J. Hep 2015

GUT MICROBIOME & NAFLD



RIFAXIMIN IN FATTY LIVER STUDY



Cobbold Unpublished

GENETICS DETERMINANTS PNPLA3 – TM6SF2

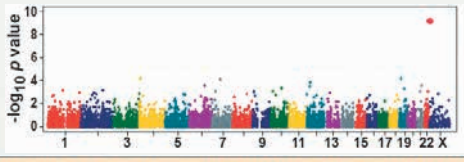


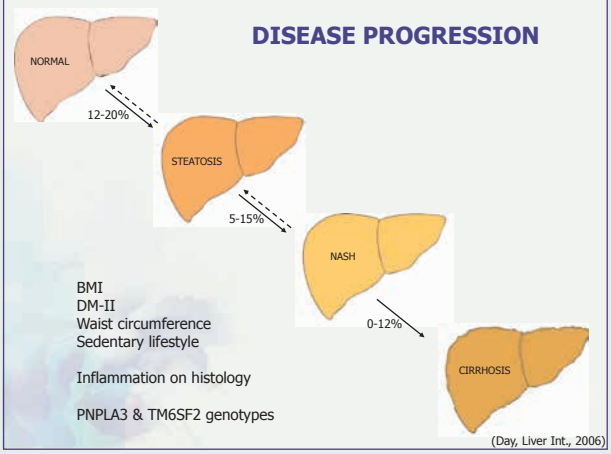
Table 1 | Multivariate analysis of association between *TM6SF2* rs58542926 genotype and fibrosis stage F0–1 (mild) versus F2–4 (advanced).

Variables	Discovery cohort (*n* = 349)		Validation cohort (*n* = 725)		Combined cohort (*n* = 1,074)	
	OR (95%CI)	*P*-value	OR (95%CI)	*P*-value	OR (95%CI)	*P*-value
TM6SF2 genotype	2.94 (1.76–4.89)	3.44×10^{-5}	1.46 (1.03–2.09)	0.0362	1.88 (1.41–2.5)	1.63×10^{-5}
PNPLA3 genotype	1.57 (1.21–2.19)	0.0086	1.32 (1.05–1.66)	0.0183	1.40 (1.16–1.69)	4.84×10^{-4}
Age	1.03 (1.01–1.06)	0.0045	1.02 (1.01–1.04)	0.0041	1.03 (1.01–1.04)	1.57×10^{-5}
Gender (female)	0.94 (0.57–1.56)	0.8297	1.81 (1.30–2.50)	4.50×10^{-4}	1.43 (1.09–1.89)	0.0096
BMI	1.05 (1.00–1.10)	0.0368	1.03 (1.01–1.05)	9.80×10^{-4}	1.04 (1.02–1.05)	3.78×10^{-5}
T2DM	2.39 (1.49–3.84)	0.0003	2.73 (1.93–3.88)	1.68×10^{-8}	2.57 (1.95–3.39)	1.78×10^{-11}

BMI, body mass index; CI, confidence interval; OR, odds ratio; T2DM, type 2 diabetes mellitus.
Additive model including age, gender, BMI, T2DM and *PNPLA3* rs738409 genotype as covariates. Discovery/validation/combined cohorts: stage F0–1 (mild) *n* = 190/159/349, stage F2–4 (advanced) *n* = 159/286/457.

Romeo Nat Gen 2008 & Liu Nat Comm 2014

DISEASE PROGRESSION



BMI
DM-II
Waist circumference
Sedentary lifestyle

Inflammation on histology

PNPLA3 & TM6SF2 genotypes

(Day, Liver Int., 2006)

NAFLD IS THE MOST IMPORTANT CAUSE OF ABNORMAL LFTS WITH NORMAL SEROLOGY

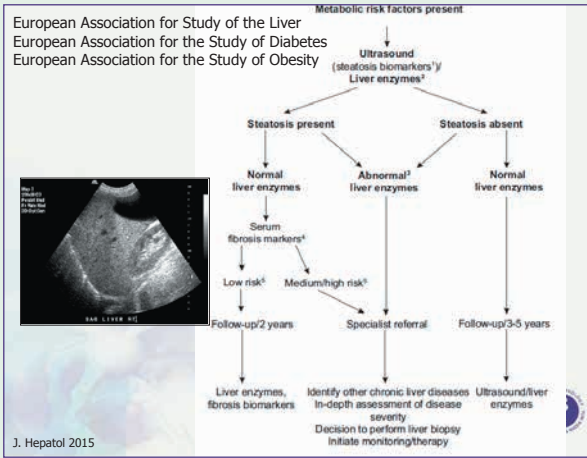
Final Diagnosis	%
NASH	34
Steatosis	32
Cryptogenic hepatitis	9
DILI	7.6
Normal	5.9
Autoimmune	1.9
Granulomas/Sarcoid	1.7
PBC	1.4
PSC	1.1

Skelly J. Hep 2001

SECONDARY HEPATIC STEATOSIS

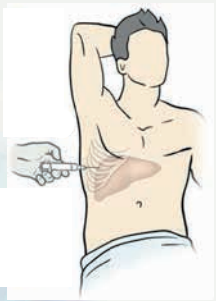
- Macrovesicular
  - Alcohol
  - Hepatitis C (Gt3)
  - Wilson's disease
  - Lipodystrophy
  - Starvation
  - Parenteral nutrition
  - Abetalipoproteinaemia
  - Drugs
    - Amiodarone, methotrexate, tamoxifen, corticosteroids
- Microvesicular
  - Reye's syndrome
  - Drugs
    - Valproate, ART
  - Acute fatty liver of pregnancy
  - Genetic disorders (eg Lysosomal acid lipase deficiency)

European Association for Study of the Liver
European Association for the Study of Diabetes
European Association for the Study of Obesity



J. Hepatol 2015

IS A BIOPSY ALWAYS NECESSARY?



- Not always necessary but may be helpful.
  - Exclude alternative/secondary pathology
  - Stratify disease progression risk

NON-ALCOHOLIC FATTY LIVER DISEASE: A SPECTRUM OF CLINICAL AND PATHOLOGICAL SEVERITY

(Matteoni *et al*, 1999: Gastroenterology 116: 1413–1419)

- Retrospective analysis of 132 patients followed for up to 18 years.

Variable	Fat alone (n = 49)	Fat + lobular inflammation (n = 10)	Fat + ballooning (n = 19)	Fat + ballooning + Mallory bodies or perisinusoidal fibrosis (n = 54)
Cirrhosis	2	0	4	14
Death	16	3	5	24
Liver-related death	1	0	1	7
	Steatosis	? NASH	NASH	

- Liver related deaths highest in groups 3 and 4.

NON-INVASIVE DIAGNOSIS OF NASH

- Steatohepatitis
  - CK18 fragments — Feldstein 2009
  - Methacetin breath test
  - Ferritin
- Fibrosis Markers
  - PIIINP
  - ELF
  - Fibrotest
  - Fibroscan

NAFLD FIBROSIS SCORE

- NAFLD Fibrosis Score=
  -1.675
  + 0.037 x **Age (years)**
  + 0.094 x **BMI (kg/m2)**
  + 1.13 x **IFG/diabetes (yes = 1, no = 0)**
  + 0.99 x **AST/ALT ratio**
  - 0.013 x **platelet (x109/l)**
  - 0.66 x **Albumin (g/dl)**.
- A score of less than -1.455 excludes fibrosis (NPV 88-93%).
- A score of greater than 0.676 predicts fibrosis (PPV 82-90%).

Angulo et al, Hepatology, 2007

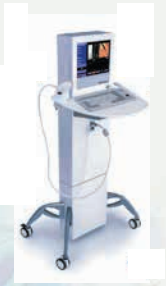
EUROPEAN LIVER FIBROSIS PANEL (ELF)

- TIMP1, Hyaluronic acid, Procollagen III peptide

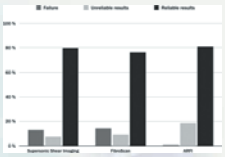
	0 Versus 1/2/3/4 Any Fibrosis	0/1 Versus 2/3/4 Moderate Fibrosis	0/1/2 Versus 3 /4 Severe Fibrosis
Simple	0.79 (0.69-0.88)	0.86 (0.78-0.94)	0.89 (0.81-0.97)
ELF	0.82 (0.73-0.90)	0.90 (0.84-0.96)	0.93 (0.88-0.98)
Simple + ELF	0.84 (0.76-0.92)	0.93 (0.88-0.99)	0.98 (0.96-1)

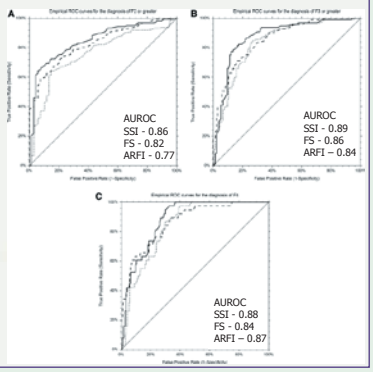
Guha. Hepatology 2008

FIBROSCAN



ELASTOGRAPHY DIAGNOSTIC PERFORMANCE





Cassinotto Hepatology 2016

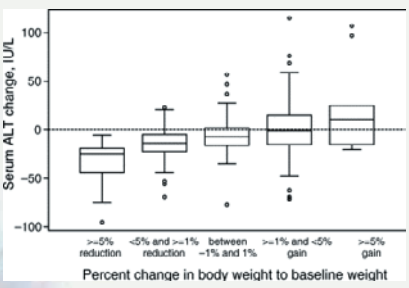
THERPEUTIC TARGETS

1. **Weight loss**
2. **Control metabolic syndrome & optimise management of components**
   - Hypertension
   - Dyslipidaemia
   - Insulin resistance/Type 2 Diabetes mellitus
3. **Prevent progression of fibrosing steatohepatitis**

LIFESTYLE MODIFICATION

- **Weight Loss**
  - **Dietary modification**
    - Dietician in clinic
    - Diabetes sister for advice
  - **Exercise**
    - Pedometers
    - Subsidised gym in hospital for group 'get fit' sessions
- **Behavioural Therapy**
  - Clear Targets
  - Positive Feedback

EFFECT OF WEIGHT LOSS ON ALT



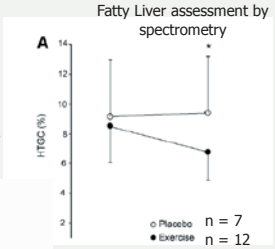
Suzuki et al. J. Hepatol 2005

REGULAR EXERCISE

Exercising improves

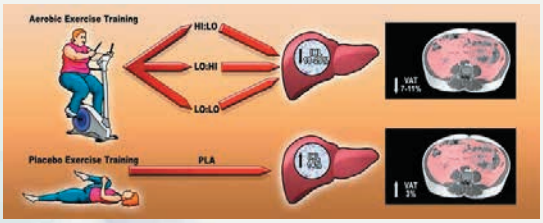
- Insulin resistance
- Steatosis
- **Independently from the weight loss**

Fatty Liver assessment by spectrometry



Johnson, Hepatology 2009
Helmerhost, Diabetes 2009

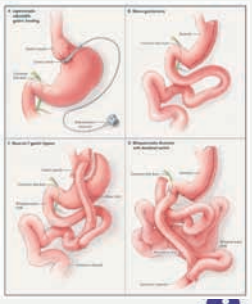
EXERCISE & VISCERAL FAT



Keating J. Hep 2015

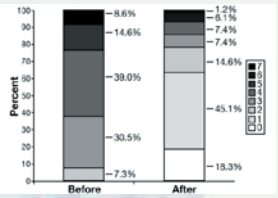
TREATING OBESITY

- **Central appetite suppressants**
  - Rimonabant (Acomplia)
    - Cannaboid receptor antagonist
    - No longer available
- **Slowing absorption**
  - Orlistat (Xenical)
    - Lipase inhibitor
    - Reduces dietary fat absorption
    - BMI >30 or >28 plus Metabolic Syndrome
    - May cause steatorrhoea
- **Bariatric Surgery**

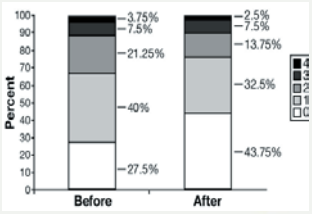


BARIATRIC SURGERY AND NAFLD

NAS Score



Fibrosis Score



Lassailly. Gastro 2015

THERPEUTIC TARGETS

1. **Weight loss**
2. **Control metabolic syndrome & optimise management of components**
   - Hypertension
   - Dyslipidaemia
   - Insulin resistance/Type 2 Diabetes mellitus
3. **Prevent progression of fibrosing steatohepatitis**

STATINS AND LFTS

- Statins do cause ^LFTs
- Statins do not cause liver failure
- Statins are **not** contraindicated in patients with
  - ^LFTs
  - Cirrhosis
  - NASH
- Statins **are** contraindicated in decompensated liver disease

- Check LFTs before starting statin therapy
- Do not monitor LFTs
  - Do as patients to report jaundice, fatigue, malaise

- An Assessment of Statin Safety by Hepatologists. Am.J. Cardiol 2006

THERPEUTIC TARGETS

1. **Weight loss**
2. **Control metabolic syndrome & optimise management of components**
   - Hypertension
   - Dyslipidaemia
   - Insulin resistance/Type 2 Diabetes mellitus
3. **Prevent progression of fibrosing steatohepatitis**

DRUG THERAPY

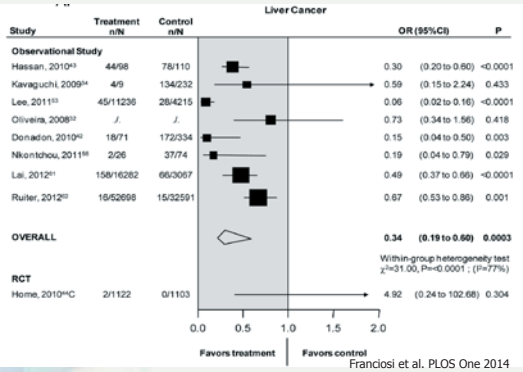
Available Now

- Insulin sensitising agents
  - Metformin
  - Glitazones (PPARg agonists)
- Anti-oxidant therapy
  - Vitamin E
- Bile Acid Metabolism
  - Ursodeoxycholic acid

In Development

- Insulin sensitising agents
  - PPAR α/δ agonists
  - GLP-1 agonists
- Bile Acid Metabolism
  - FXR agonists
- Anti-inflammatory
  - CCR2/CCR5 Inhibition
- Anti-fibrotics
  - Lysyl Oxidase antibody

METFORMIN & LIVER CANCER



Franciosi et al. PLOS One 2014

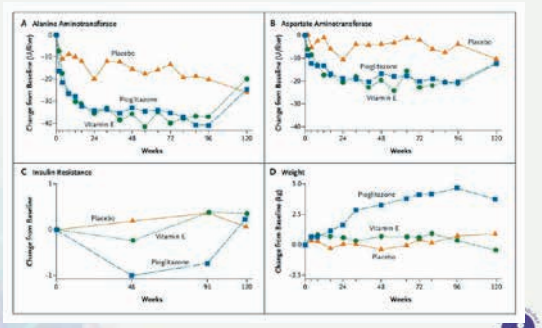
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pioglitazone, Vitamin E, or Placebo for Nonalcoholic Steatohepatitis

Arun J. Sanyal, M.D., Naga Chalasani, M.B., B.S., Kris V. Kowdley, M.D., Arthur McCullough, M.D., Anna Mae Diehl, M.D., Nathan M. Bass, M.D., Ph.D., Brent A. Neuschwander-Tetri, M.D., Joel E. Lavine, M.D., Ph.D., James Tonascia, Ph.D., Aynur Unalp, M.D., Ph.D., Mark Van Natta, M.H.S., Jeanne Clark, M.D., M.P.H., Elizabeth M. Brunt, M.D., David E. Kleiner, M.D., Ph.D., Jay H. Hoofnagle, M.D., and Patricia R. Robuck, Ph.D., M.P.H., for the NASH CRN

PIVENS: ALT, AST, Insulin Resistance, and Weight, According to Study Group.



SANYAL AJ ET AL. N ENGL J MED 2010;362:1675-1685.

PIVENS: Histological Outcomes.

Variable	Placebo	Vitamin E	Pioglitazone	P Value*	
				Vitamin E vs. Placebo	Pioglitazone vs. Placebo
Primary outcome†					
No. of subjects randomly assigned	83	84	80		
Subjects with improvement (%)	19	43	34	0.001	0.04
Changes from baseline in histologic features					
No. of subjects with biopsy specimens at baseline and 96 wk	72	80	70		
Steatosis					
Subjects with improvement (%)	31	54	69	0.005	<0.001
Mean change in score	−0.1	−0.7	−0.8	<0.001	<0.001
Lobular inflammation					
Subjects with improvement (%)	35	54	60	0.02	0.004
Mean change in score	−0.2	−0.6	−0.7	0.008	<0.001
Hepatocellular ballooning					
Subjects with improvement (%)	29	50	44	0.01	0.08
Mean change in score	−0.2	−0.5	−0.4	0.03	0.01
Total NAFLD activity score (mean change)	−0.3	−1.9	−1.9	<0.001	<0.001
Fibrosis‡					
Subjects with improvement (%)	31	41	44	0.24	0.12
Mean change in score	−0.1	−0.3	−0.4	0.19	0.10
Resolution of definite nonalcoholic steatohepatitis (% of subjects)	21	36	47	0.05	0.001

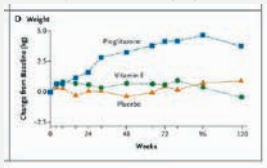
SANYAL AJ ET AL. N ENGL J MED 2010;362:1675-1685.

Why not Pioglitazone/Vitamin E for All NAFLD Patients?

Neither drug tested in diabetics
No data on efficacy/safety in cirrhotics

Vitamin E
- Increased risk of haemorrhagic stroke
- Increased risk of prostate cancer
- Increased overall mortality

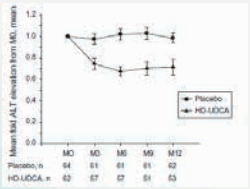
Pioglitazone
- Increased weight
- Long term safety questions

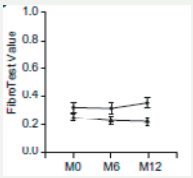


URSODEOXYCHOLIC ACID

- Pleotropic Effects
  - Choloretic
  - Anti-apoptotic
  - Reduced mitochondrial permeability
  - Anti-oxidant
  - Reduced TNFα
  - Reduced TGFβ
- Reduced liver damage in animal models of NASH
  - MCD mouse
- Extensive human use
  - Safe

UDCA (28-35 MG/KG)





Parameter	HD-UDCA	Placebo	p
Serum glucose level	-2.2	+3.9	0.002
HbA1c level	-2.3	+5.2	<0.001
Insulin level	-19	-0.2	0.038
HOMA score	-20	+6	<0.009

*Percent relative change between baseline median values and M12.

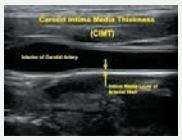
Ratziu J.Hep 2011

URSODEOXYCHOLIC ACID

Study	Liver function improvement	Histology alleviation
Monotherapy		
Laurin et al. [24]*	ALT (−30%), ALP (−8%) and γGT (−45%)	steatosis improved
Lindor et al. [25]	ALT in −31% vs. −29%	steatosis in −18% vs. −14%; inflammation in −0 vs. −0.1; fibrosis in 0 vs. 0
Dufour et al. [20]	ALT in −36% vs. −2%	steatosis in −13% vs. −14%, inflammation in −0.8 vs. −0.02 fibrosis in +0.3 vs. +0.4
Kiyici et al. [26]	ALT in −26% vs. −43% ALT in 76.0 vs. 55.1, γGT in 47.8vs 32.2	liver density +20% vs. +35% (in UDCA group between after and before therapy)
Hong Qian, et al. [32]	Effective ratio 24/26 vs. 25/27	not mentioned
Zhu Hong-juan [27]	liver function and symptom in 25/30 vs. 15/30	not mentioned
Ratziu et al. [28]	ALT in −28% vs. −2% γGT in −51% vs. +19%	fibrosis in −11% vs. +10%*
Leuschner et al. [29]	ALT in −41% vs. −35%	Brunt score in −14% vs. −14% NAS activity score in −21% vs. −18%
UDCA combined with other drugs		
Dufour et al. [20]	ALT in −42% vs. −2% AST in −30% vs. +6%	steatosis in −1.4 vs. −0.5; inflammation in −2.2 vs. −0.8
Zhuang Xue-shan [30]	Effective rate 36/40 vs. 29/42	26/40 vs. 17/42 in steatosis (ultrasound)
Sun Yan [31]	ALT in −79 vs. −72, AST in −31 vs. −8, Effective rate 60/76 vs. 37/61	not mentioned
Lv Hong [33]	ALT in −45.9 vs. −16.1 AST in −40.1 vs. −29.5	no report in histology
Liu Zhi-ye [34]	Effective rate 86/96 vs. 38/54	no report in histology

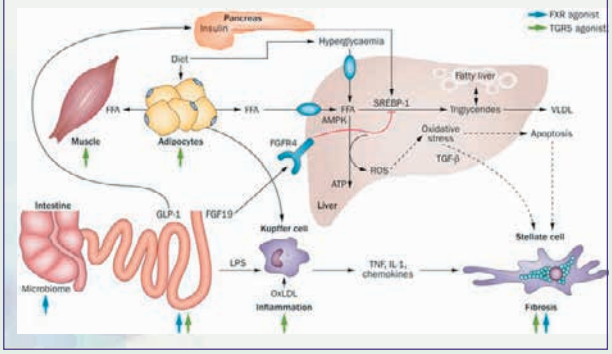
UDCA IMPROVES METABOLIC PARAMETERS IN NASH

	Before therapy (N=30)	After therapy (N=30)	P
BMI (kg/m²)	30.8±4.7	30.5±4.6	0.134
Waist circumference (cm)	106±11.1	105.9±11.6	0.854
HOMA	3.4±1.9	2.8±1.6	0.041
AST (U/dl)	49 (37–66)	28.5 (24–31.5)	0.001
ALT (U/dl)	84 (59–118.5)	36 (26.5–48)	0.001
GGT (U/dl)	47 (32.5–65)	27.5 (22–36)	0.001
ALP (U/dl)	80.5 (65.5–100)	88 (71.5–106.5)	0.234
TG (mg/dl)	138.7±46.7	129±45.1	0.194
TK (mg/dl)	190.3±22.6	186.9±28.4	0.448
LDL (mg/dl)	118.1±20.3	113.9±26.8	0.368
HDL (mg/dl)	42.9±7.1	45.5±9.8	0.037
VLDL (mg/dl)	26.9±9.2	26.3±8.5	0.696
Apo A1 (mg/dl)	127.6±17.7	135.9±22.2	0.026
Apo B (mg/dl)	102.50±29.9	102.57±25.05	0.986
Apo B/A1 ratio	0.81±0.25	0.74±0.22	0.078
CIMT (mm)	0.559±0.152	0.479±0.121	0.001



Coskun EJGH 2015

FXR AGONISTS



FXR AGONIST IN NASH – FLINT TRIAL

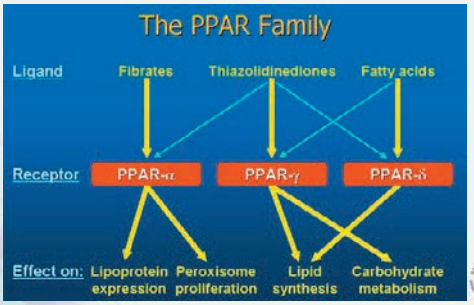
	Obeticholic acid	Placebo	Relative risks or mean changes from baseline* (95% CI) (obeticholic acid vs placebo)	p value*
Primary outcome†				
Number of patients at risk‡	110	109		
Patients with improvement	50 (45%)	23 (21%)	2·2 (1·4 to 3·3)	0·0002
Changes from baseline in histological features				
Number of patients with biopsy specimens at baseline and 72 weeks	102	98		
Resolution§ of definite non-alcoholic steatohepatitis	22 (22%)	13 (13%)	1·7 (0·9 to 3·2)	0·08
Fibrosis¶				
Patients with improvement	36 (35%)	19 (19%)	2·0 (1·2 to 3·4	0·004
Change in score	−0·2 (1·1)	0·1 (0·9)	−0·3 (−0·6 to −0·1)	0·01
Total NAFLD activity score				
Change in score	−1·7 (1·8)	−0·7 (1·8)	−0·9 (−1·3 to −0·5)	<0·0001
Hepatocellular ballooning				
Patients with improvement	47 (46%)	30 (31%)	1·5 (1·0 to 2·1)	0·03
Change in score	−0·5 (0·6)	−0·2 (0·9)	−0·2 (−0·5 to 0·0)	0·03
Steatosis				
Patients with improvement	62 (61%)	37 (38%)	1·6 (1·2 to 2·2)	<0·001
Change in score	−0·8 (1·1)	−0·4 (0·8)	−0·4 (−0·6 to −0·2)	0·0004
Lobular inflammation				
Patients with improvement	54 (53%)	34 (35%)	1·6 (1·1 to 2·2)	0·006
Change in score	−0·5 (0·8)	−0·2 (0·9)	−0·3 (−0·5 to −0·1)	0·0006

Key side effects
- Pruritus
- Increased LDL cholesterol

Neuschwander-Tetri. Lancet 2015

PPARA/Δ AGONIST

Elafibrinor



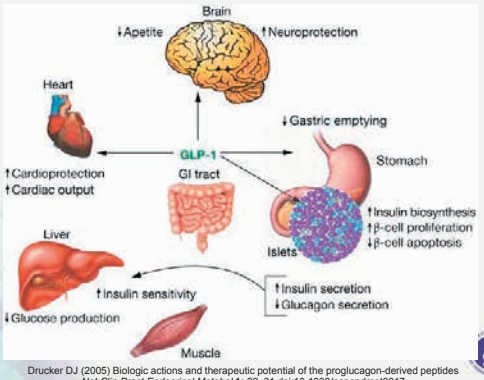
ELAFIBRANOR IN NASH

NAS	n	Placebo, n (%)	Elafibranor 80 mg, n (%)	Elafibranor 120 mg, n (%)	OR (95% CI)[a]	P value[a]
Protocol-defined primary outcome						
Total	274	92 (17)	93 (23)	89 (21)	1.53 (0.70–3.34)	.280
NAS ≥4 (moderate and severe)	234	76 (11)	83 (20)	75 (20)	3.16 (1.22–8.13)	.018
NAS 3 (mild)	40	16 (50)	10 (40)	14 (29)		
Modified definition of response						
Total	274	92 (12)	93 (13)	89 (19)	2.31 (1.02–5.24)	.045
NAS ≥4 (moderate and severe)	234	76 (9)	83 (13)	75 (19)	3.52 (1.32–9.40)	.013
NAS 3 (mild)	40	16 (25)	10 (10)	14 (21)		

[a]Elafibranor 120 mg vs placebo, direct treatment effect.

Ratziu Gastro 2016

ACTIONS OF GLUCAGON-LIKE PEPTIDE 1



Drucker DJ (2005) Biologic actions and therapeutic potential of the proglucagon-derived peptides *Nat Clin Pract Endocrinol Metabol* **1**: 22–31 doi:10.1038/ncpendmet0017

	Liraglutide	Placebo	Relative risks or mean changes (95% CI) from baseline to 48 weeks (liraglutide vs placebo)	p value*
Primary outcome				
Number of patients with paired liver biopsies	23	22	..	..
Patients with resolution of non-alcoholic steatohepatitis	9 (39%)	2 (9%)	4·3 (1·0 to 17·7)	0·019
Changes from baseline in histopathological parameters				
Total NAFLD activity score				
Change in score	−1·3 (1·6)	−0·8 (1·2)	−0·5 (−1·3 to 0·3)	0·24
Patients with improvement	17 (74%)	14 (64%)	1·2 (0·8 to 1·7)	0·46
Hepatocyte ballooning score				
Mean change	−0·5 (0·7)	−0·2 (0·6)	−0·3 (−0·7 to 0·1)	0·15
Patients with improvement	14 (61%)	7 (32%)	1·9 (1·0 to 3·8)	0·05
Steatosis				
Change in score	−0·7 (0·8)	−0·4 (0·8)	−0·2 (−0·6 to 0·2)	0·32
Patients with improvement	19 (83%)	10 (45%)	1·8 (1·1 to 3·0)	0·009
Lobular inflammation				
Change in score	−0·2 (0·6)	−0·2 (0·5)	−0·01 (−0·3 to 0·3)	0·97
Patients with improvement	11 (48%)	12 (55%)	0·9 (0·5 to 1·6)	0·65
Kleiner fibrosis stage				
Change in score	−0·2 (0·8)	0·2 (1·0)	−0·4 (−0·8 to 0·1)	0·11
Patients with improvement	6 (26%)	3 (14%)	1·9 (0·5 to 6·7)	0·46†
Patients with worsening	2 (9%)	8 (36%)	0·2 (0·1 to 1·0)	

Newsome Lancet 2016

SUMMARY

- NAFLD is not a benign disease
  - Increased liver mortality
  - Increased cardiovascular disease
- Full assessment requires
  - Evaluation of fibrosis
  - Identification of all clinical manifestations of metabolic syndrome
- Management should focus on
  - Weight loss
  - Cardiovascular / Cerebrovascular risk factors
  - Drug therapy

NAFLD AND ALCOHOLIC LIVER DISEASE: SIMILARITIES AND DIFFERENCES

Marina V. MAEVSKAYA

Sechenov First Moscow State Medical University, Moscow; Russian Federation

Alcohol and non-alcoholic fatty liver disease (NAFLD) are two factors with the potential to keep level of liver cirrhosis relatively high in European countries (1, 2). According to the population-based study in Russia with the main goal to screen the Moscow citizens for the prevalence of liver disease published in 2014 alcoholic liver disease (ALD) takes the 2nd place after NAFLD (3).

The main risk factor for NAFLD is obesity for ALD – harmful alcohol consumption and alcohol dependence. Obesity (consequence of binge eating) and harmful alcohol consumption besides liver injury usually associate with behavioural disorders (such as anxiety, depression etc.), high blood pressure, dyslipidaemia, heart diseases, liver cancer and so on. Thus, multidisciplinary team is required for the successful patients' management. The pathogenesis of NAFLD and ALD is similar: high prevalence of SIBO, increased intestinal permeability and bacterial overgrowth, activation an inflammatory cascade through both TLR4-dependent and TLR-4-independent pathways (4, 5). But the main difference between NAFLD and ALD is clinical course. NAFLD including NASH usually is asymptomatic on any stage of disease except advanced liver cirrhosis. In contrast the short-term mortality among patients with severe ALD exceeds 30%. Jaundice is the main presenting feature of severe alcoholic hepatitis (or alcoholic steatohepatitis – ASH). It may be associated with fever with or without infection, weight loss and malnutrition, large tender liver and signs of liver failure and kidney insufficiency (hepatorenal syndrome type 1). Despite different clinical course NASH and ASH have similar histological features, which are the following: a coexistence of steatosis, hepatocyte ballooning, and an inflammatory infiltrate with PMNs. To identify patients with ASH at high risk of early death (1–3 months after disease onset) several prognostic models have been designed: the Maddrey discriminant function (DF), the MELD (Model for End-Stage Liver Disease), the GAHS (Glasgow ASH Score) and the ABIC score (age, serum bilirubin, INR, and serum creatinine score). Corticosteroids improves the short-term mortality in patients with ASH and Maddrey's discriminant function ≥ 32 (severe alcoholic hepatitis) and should be used as a first-line treatment unless concomitant gastrointestinal bleeding, active infection, renal failure, or pancreatitis (2, 6). As for the NASH corticosteroids are never in use. Following the recent publications including meta-analysis UDCA therapy is effective in NASH as a monotherapy as in combination with other drugs (for instance, vit E) and improves liver function, steatosis and inflammation (7). There are no exact recommendations for the treatment of patients with mild/moderate ASH except abstinence and nutrition support for undernourished patients (2). Some further investigations with SAMe, UDCA are needed.

Both NAFLD and ALD are multifaceted diseases and require an interdisciplinary approach.

Literature:

1. Global status report on noncommunicable disease 2010, *http://www.who.int/nmh/publications/ncd_report_full_en.pdf*
2. EASL Clinical Practical Guidelines: Management of Alcoholic Liver Disease. Journal of Hepatology; 2012; 57: 399–420.
3. Komova A., Maevskaya M., Ivashkin V. Prevalence of liver disease in Russia's largest city: a population-based study. American Journal of Clinical Medical Research, 2014; 2(5): 99–102.
4. Hartmann P., Chen W., Schnabl B. The intestinal microbiome and the leaky gut as therapeutic targets in alcoholic liver disease. Front Physiol. 2012 Oct 11; 3: 402. doi: 10.3389/fphys.2012.00402
5. Caricilli A.M., Saad M.J. The role of gut microbiota on insulin resistance. Nutrients 2013; 5: 829–851.
6. Mathurin P., O'Grady J., Carithers R.L., Phillips M., Louvet A., Mendenhall C.L., *et al*. Corticosteroids improve short-term survival in patients with severe alcoholic hepatitis: meta-analysis of individual patient data. Gut 2011; 60: 255–260.
7. Xiang Z., Chen Y., Ma K., Ye Y., Zheng L., Yang Y., Li Y., Xi J. The role of Ursodeoxycholic acid in non-alcoholic steatohepatitis: a systematic review. BMC Gastroenterology 2013, 13: 140 *http://www.biomedcentral.com/1471-230X/13/140*

Maevskaya M.V. NAFLD and alcoholic liver disease: Similarities and differences. In: *11th International Symposium of Gastroenterology, Saint Petersburg, Russia, 12–14 May 2016*. [online].
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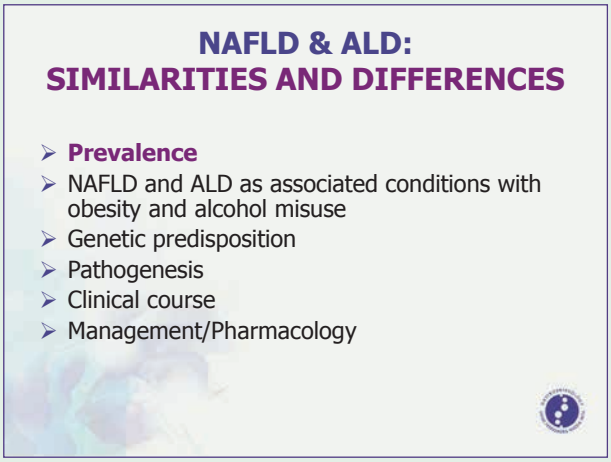
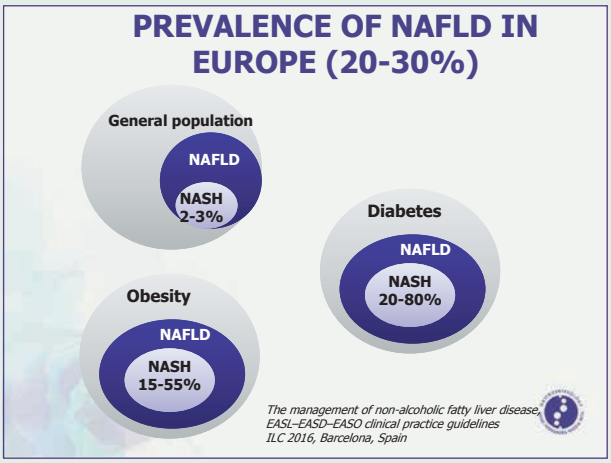
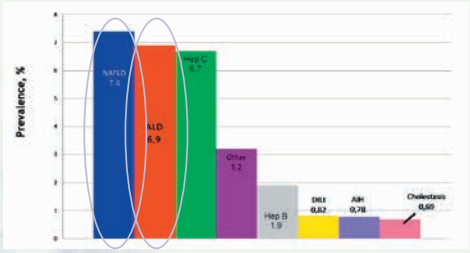




NAFLD & ALD
PREVALENCE IN RUSSIA (GENERAL POPULATION – MOSCOW CITIZENS): SIMILARITIES



Liver disease prevalence according to preliminary diagnosis in Moscow citizens (n=4768)

Комова А.Г., Маевская М.В., Ивашкин В.Т., РЖГГ, 2014. – Т.24.- №5. – с. 36-41.
Komova A., Maevskaya M., Ivashkin V.,
American Journal of Clinical Medical Research, 2014, Vol.2, No. 5, 99-102.

NAFLD & ALD
SIMILARITIES AND DIFFERENCES

- Prevalence
- **NAFLD and ALD as associated conditions with obesity and alcohol misuse**
- Genetic predisposition
- Pathogenesis
- Clinical course
- Management/Pharmacology

NAFLD & ALD
BEHAVIOR SIMILARITIES IN BOTH DISORDERS

Behavior disorders:
Binge eating
(stress, anxiety, depression, genetic predisposition etc.)
↓
Obesity
↓
NAFLD

Behavior disorders:
Chronic alcohol consumption: binge, continuous etc.
(stress, anxiety, depression, genetic predisposition etc.)
↓
Harmful alcohol consumption
Alcohol dependence
↓
ALD

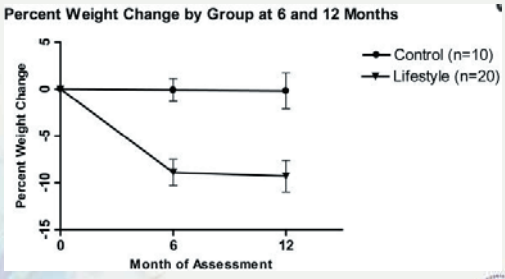
NAFLD & ALD
BEHAVIOR SIMILARITIES IN BOTH DISORDERS

Behavior disorders:
Binge eating
(stress, anxiety, depression, genetic predisposition etc.)
↓
Obesity
↓
NAFLD

Behavior disorders:
Chronic alcohol consumption: binge, continuous etc.
(stress, anxiety, depression, genetic predisposition etc.)
↓
Harmful alcohol consumption
Alcohol dependence
↓
ALD

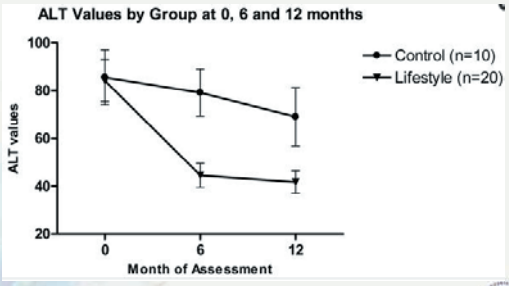
→ **Multidisciplinary team for patients management** ←

RANDOMIZED CONTROLLED TRIAL TESTING THE EFFECTS OF WEIGHT LOSS ON NASH



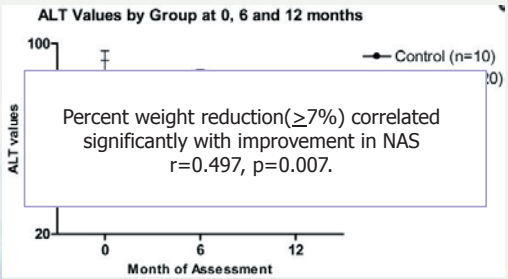
Promrat K et al., Hepatology, 2010

RANDOMIZED CONTROLLED TRIAL TESTING THE EFFECTS OF WEIGHT LOSS ON NASH



Promrat K et al., Hepatology, 2010

RANDOMIZED CONTROLLED TRIAL TESTING THE EFFECTS OF WEIGHT LOSS ON NASH



Promrat K et al., Hepatology, 2010

COGNITIVE-BEHAVIORAL TREATMENT OF NON-ALCOHOLIC FATTY LIVER DISEASE: A PROPENSITY SCORE-ADJUSTED OBSERVATIONAL STUDY

Cognitive-Behavioral Treatment (CBT) group – 68 pts
CBT program aimed at weight loss, increased physical activity, based on 13 group sessions

Non – CBT group – 82 pts
recommendations for diet and physical activity

Treatment goals: weight loss ≥ 7% initial b.w., normalization of liver enzymes, improved parameters of metabolic syndrome)
Follow up time – 2 years

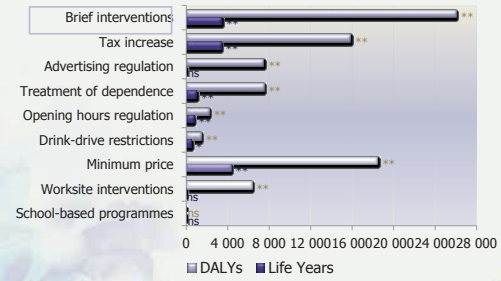
Weight loss
ALT level ↓
HOMA-R ↓

p<0,05

Weight loss
ALT level ↓
HOMA-R ↓

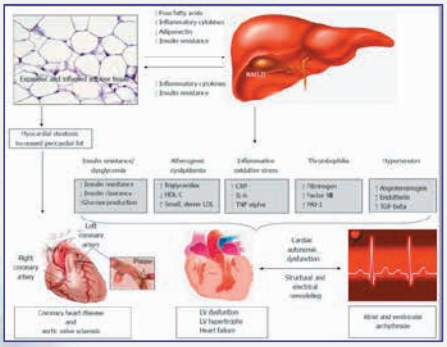
Moscatiello S et al, http://amsacta.unibo.it/3096/1/Obesity_2011_19_763_70.pdf

ALCOHOL AND THE ECONOMICS ON PUBLIC HEALTH
HEALTH OUTCOMES. CZECH REPUBLIC



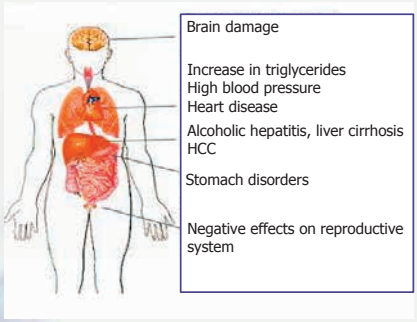
Franco Sassi, *OECD Public Health Programme, http://www.keepeek.com/Digital-Asset-Management/oecd/social-issues-migration-health/tackling-harmful-alcohol-use/summary/english_acc5aeb2-en#page2*

NAFLD: A MULTIFACTORIAL DISEASE.



Ballestry S et al, World J Gastroenterol. 2014 Feb 21; 20(7): 1724–1745.

ALD: A MULTIFACTORIAL DISEASE



Brain damage

Increase in triglycerides
High blood pressure
Heart disease

Alcoholic hepatitis, liver cirrhosis
HCC

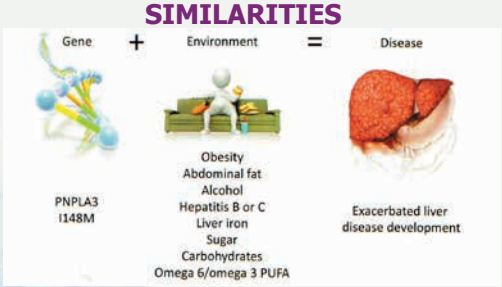
Stomach disorders

Negative effects on reproductive system

NAFLD & ALD:
SIMILARITIES AND DIFFERENCES

- Prevalence
- NAFLD and ALD as associated conditions with obesity and alcohol misuse
- **Genetic predisposition**
- Pathogenesis
- Clinical course
- Management/Pharmacology

GENETIC PREDISPOSITION TO NAFLD AND ALD
SIMILARITIES

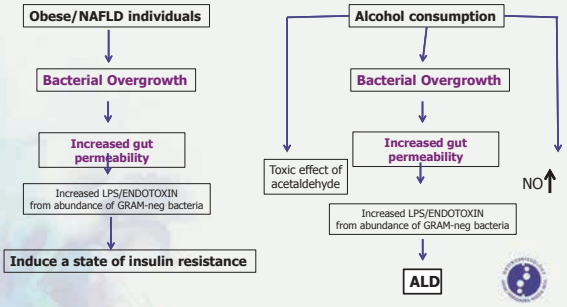


Kahali B. et al, Seminars in Liver Disease, 2015

NAFLD & ALD:
SIMILARITIES AND DIFFERENCES

- Prevalence
- NAFLD and ALD as associated conditions with obesity and alcohol misuse
- Genetic predisposition
- **Pathogenesis**
- Clinical course
- Management/Pharmacology

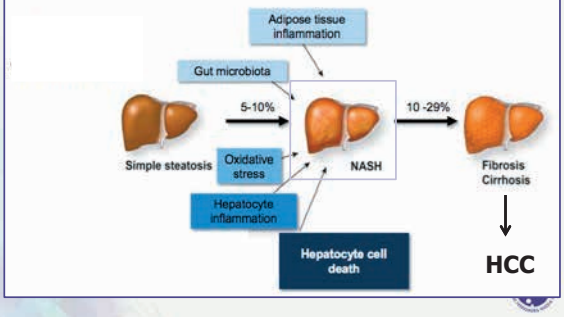
NAFLD & ALD
PATHOGENIC SIMILARITIES IN BOTH DISORDERS
GUT MICROBIOTA AND LIVER



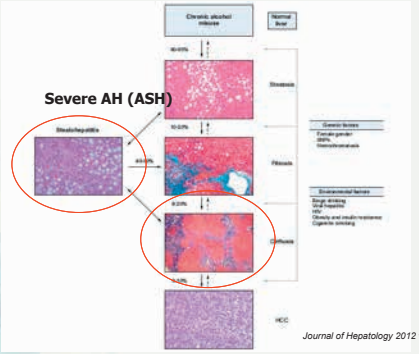
NAFLD & ALD:
SIMILARITIES AND DIFFERENCES

- Prevalence
- NAFLD and ALD as associated conditions with obesity and alcohol misuse
- Genetic predisposition
- Pathogenesis
- **Clinical course**
- Management/Pharmacology

CLINICAL COURSE OF NAFLD & ALD
SIMILARITIES AND DIFFERENCES
NAFLD CLINICAL COURSE



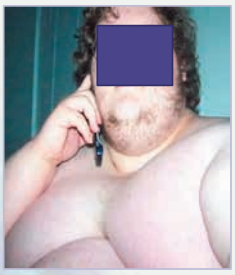
CLINICAL COURSE OF NAFLD & ALD
SIMILARITIES AND DIFFERENCES
ALD CLINICAL COURSE



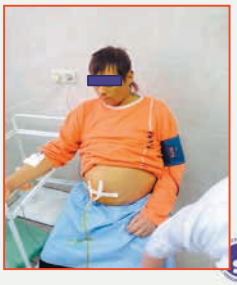
Journal of Hepatology 2012 vol. 57 j 399–420

NAFLD & ALD DIFFERENCES
SHORT-TERM PROGNOSIS

NAFLD/NASH – largely excellent (no signs of liver failure)



Adverse in pts. with severe AH (signs of liver failure)



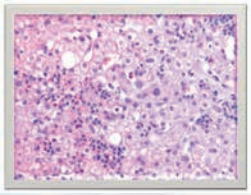
DISEASE SEVERITY: CLINICAL SCORES TO DIAGNOSE ASH

- **Maddrey Discriminant Function (DF)** *Gastroenterology 1978*
  - PT, control PT and serum bilirubin
  - Score ≥32 is associated with a high short-term mortality
- **Model for End-Stage Liver Disease (MELD)** *Hepatology 2005*
  - Bilirubin, INR, creatinine
  - MELD > 18 to 21
- **Glasgow Alcoholic Hepatitis Score (GAHS)** *Gut 2005*
  - Age, bilirubin, BUN, PT, peripheral WBC
  - Pts with GAH ≥ 9 may benefit from glucocorticoids
- **ABIC score**
  - Age, serum bilirubin, INR, and serum creatinine score *Am J Gastroenterol 2008*
- **Lille Model**
  - Age, renal function, albumin, PT, bilirubin evolution at day 7 comparing with baseline bilirubin level *Hepatology 2007*
    > 0.45 suggests the patient is not responding to steroids
    > 0.56 - null responders

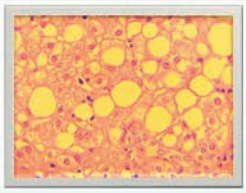
Gut 2011

HISTOLOGY SIMILARITIES

ASH

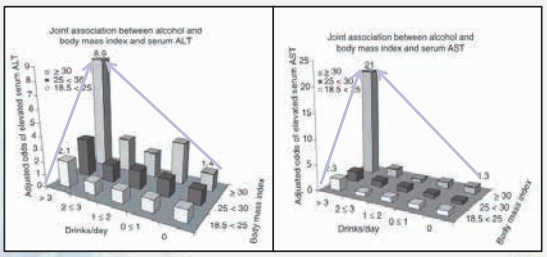


NASH



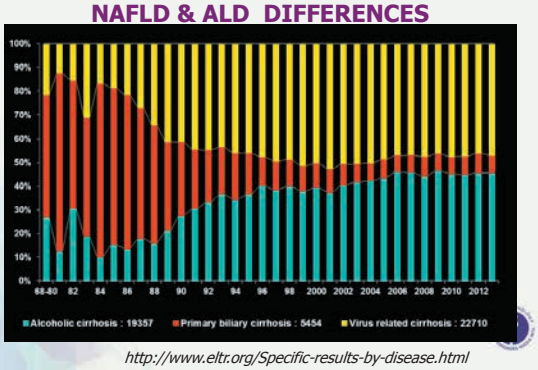
Courtesy Prof. Nekrasova, 1st Moscow Medical University

SYNERGISTIC ASSOCIATION BETWEEN ALCOHOL INTAKE, BMI AND WITH LIVER FUNCTIONAL TESTS (ALT&AST)



Loomba R et al, Aliment Pharmacol Ther, 2009, 30, 1137-1149

EVOLUTION OF INDICATIONS OF CIRRHOSIS FOR LIVER TRANSPLANTATION IN EUROPE
NAFLD & ALD DIFFERENCES



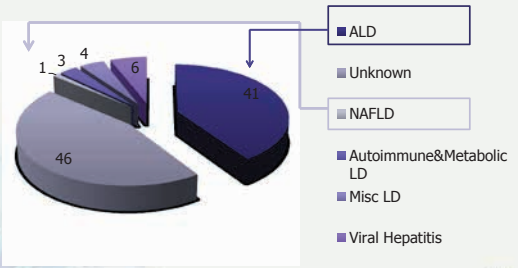
http://www.eltr.org/Specific-results-by-disease.html

ALCOHOLIC LIVER DISEASES

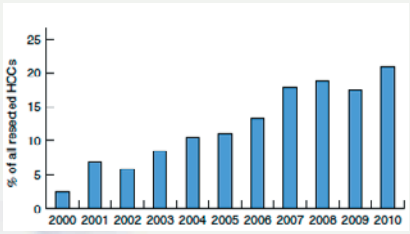
- Alcoholic liver disease accounts for 70 to 80% of all directly recorded mortality from alcohol
- Alcohol is strongly associated with overall liver cirrhosis rates, with 47.9% of liver cirrhosis deaths

Rehm J et al, J. of Hepatology 2013 vol. 59 j 160–168

AETIOLOGY OF GLOBAL LIVER DEATHS 2000-2012 (%)
NAFLD & ALD DIFFERENCES



HCC IN PATIENTS WITH METABOLIC SYNDROME



	Abnormal liver (n=24)	Normal liver (n=38)
mortality	18%	0%
complications	42%	13%

Cauchy, BJ Surg 2012

GEOGRAPHIC DISTRIBUTION OF HCC RISK FACTORS
THE BRIDGE COHORT STUDY

Risk Factors N (%)	N. America N=2243	Europe N=3466	China N=8538	Taiwan N=1580	S. Korea N=1172	Japan N=446
HBC	522 (23)	362 (10)	6575 (77)	987 (63)	884 (75)	64 (14)
HCV	876 (39)	1590 (46)	255 (3)	489 (31)	112 (10)	284 (64)
ALD	471 (21)	1290 (37)	416 (5)	66 (4)	110 (9)	59 (13)
NASH	275 (12)	334 (10)	53 (1)	84 (5)	68 (6)	9 (2)

Park JH et al, Liver Int. 2015; 35, 2155-66

NAFLD AND HEPATOCELLULAR CARCINOMA

- Risk factors
  - Diabetes
  - Older age
  - Presence of cirrhosis
- Incidence of HCC 2-3% per year
- Carcinogenesis can occur in the absence of advanced fibrosis in patients with NAFLD

Sanyal, Curr Med Res Opin 2010
Loomba, Nat Rev Gastroenterol Hepatol 2013

NAFLD & ALD: SIMILARITIES AND DIFFERENCES

- Prevalence
- NAFLD and ALD as associated conditions with obesity and alcohol misuse
- Genetic predisposition
- Pathogenesis
- Clinical course
- **Management/Pharmacology**

TREATMENT OPTIONS

- **NAFLD & ALD Similarities**
  - life style modification: behavior interventions (multidisciplinary team), physical activity
- **NAFLD & ALD Differences**
  - Drug therapy of NASH and severe ASH

DRUG TREATMENT
NAFLD & ALD DIFFERENCES

Treatment of Obesity
- psychosocial interventions and pharmacological therapy (orlistat)
- bariatric surgery

Treatment of NAFLD
- **Insulin Sensitizers** (Metformin, Pioglitazone)

-Liver-directed pharmacology: Cytoprotective/Antioxidants - UDCA, Vit. E

-New treatment (?): Debate on GLP, Obeticholic acid and Elafibranor

Agreed outcome:
NASH resolution,
no worsening of fibrosis

Treatment of Alcohol Use Disorder
- psychosocial interventions and pharmacological therapy (baclofen)

Treatment oh ALD
- Prednisolone for severe Alcoholic Hepatitis (ASH)

Cytoprotective/Antioxidants
- UDCA, SAMe (?)

-New treatment regimens is needed

Agreed outcome:
Achievement and maintenance of total alcohol abstinence.
AH (ASH) resolution,
improvement in short-term mortality, no worsening of fibrosis

THE EFFECTS OF URSODEOXYCHOLIC ACID (UDCA) IN THE TREATMENT OF NASH: META-ANALYSIS

- 12 randomized clinical trials, involving 1160 subjects, were selected
- 7 of 12 assessed the effects of UDCA Monotherapy
- 5 of 12 testing combinations of UDCA with vitamin E, polyene phosphatidylcholine, silymarin, glycyrrhizin and tiopronin
- The duration of therapy ranged from 3 to 24 months

Xiang et al. BMC Gastroenterology 2013, 13:140

THE EFFECTS OF URSODEOXYCHOLIC ACID (UDCA) IN THE TREATMENT OF NASH: META-ANALYSIS

Results

Monotherapy

UDCA significantly improved liver function in five studies and improved steatosis and fibrosis in two studies

Combination therapy

All five studies assessing UDCA combination therapy showed significant improvements liver function, while two studies also improved steatosis and inflammation. One study of high-dose UDCA ((23–35 mg/kg/d) showed significant improvements in ALT, γGT and liver fibrosis

Conclusion

UDCA therapy is effective in NASH as a monotherapy as in combination with other drugs

Xiang et al. BMC Gastroenterology 2013, 13:140

ACTION OF UDCA ON THE CAROTID INTIMA MEDIA THICKNESS (CIMT). APOLIPOPROTEIN A1, APOLIPOPROTEIN B AND B/A1 RATIO IN NASH

- **Prospective study**: 30 patients with biopsy-proven NASH and 25 healthy adults as a control group
  Patients with NASH received UDCA 15 mg/kg/day for 6 months.
  BMI, waist circumference, homeostasis model assessment, lipids, apo A1, apo B, apo B/A1 ratios, and CIMT were analyzed before and after the treatment period.
- **Results**:
  Liver enzymes decreased gradually
  statistically significant **decrease in insulin resistance**
  (HOMA: from3.4±1.89 to 2.06±1.68 **(*P*<0.001)**
  statistically significant **increase in high-density lipoprotein**(42.9±7.1 vs. 45.5±9.8; *P*=0.037)
  statistically significant **increase in Apo1** (127.6±17.7 vs. 135.9±22.2; *P*=0.02)
  statistically significant **decrease in carotid intima media thickness** (0.56±0.15 vs. 0.47±0.12; *P*=0.001)
  trend to the decrease apo B/A1 ratio
  No significant changes in IMB and waist circumference
  No significant changes in the mean triglyceride, total cholesterol, low-density lipoprotein, or apo B levels

Conclusion: UDCA treatment in NASH patients resulted in statistically significant reductions in the mean CIMT due from decreased insulin resistance and increased serum high-density lipoprotein–apo A1 levels.

Ozel Coskun, Banu D.et al.,
European Journal of Gastroenterology & Hepatology:
February 2015 - Volume 27 - Issue 2 - p 142–149

CONCLUSION (1)

- NAFLD & ALD are common worldwide
- NAFLD & ALD are strongly associated with obesity and excessive alcohol consumption.
- NAFLD & ALD are the spectrum of disease: steatosis, hepatitis, fibrosis/cirrhosis and HCC. Short-term prognosis is usually excellent in NASH, but adverse in patients with severe ASH. Carcinogenesis can occur in the absence of advanced fibrosis in patients with NAFLD
- NAFLD & ALD are frequently accompanied by extrahepatic complications. NAFLD is an independent risk factor for cardiovascular disease

CONCLUSION (2)

- GWAS of NAFLD & ALD suggested that a *PNPLA3* SNP, I148M (rs738409 C/G) is associated with increased hepatic fat content and disease progression
- A population-based study found that ALD contributed to liver-related mortality whereas the leading causes of death in patients with NAFLD were cardiovascular disease
- Treatment options for NAFLD/NASH & ALD/ASH are similar concerning life style modification (behavior interventions), but drug treatment is different – UDCA and Vit E for NASH; Prednisolon for severe ASH
- UDCA is promised as a cytoprotective/antioxidant compound in patients with NAFLD/NASH, especially in MS

NAFLD AND CARDIOVASCULAR COMORBIDITY

Oxana M. DRAPKINA

State Scientific Research Institute of Preventive Medicine, Moscow; Russian Federation

Non-alcoholic fatty liver disease (NAFLD) may be considered as an additional sixth criterion of metabolic syndrome (MS). Insulin resistance plays a key role in the MS pathogenesis; particularly, it underpins all manifestations of this syndrome including cardiovascular conditions.

However, as it has currently been reported in some studies, NAFLD is not just one of the MS manifestations: it is an individual and independent factor increasing the risk of cardiovascular complications by approximately 25%. The report shows in detail which mechanisms of NAFLD lead to such an effect. One of the main mechanisms of NAFLD influence on the cardiovascular event risk is the fact that it modifies the cholesterol metabolism processes increasing its synthesis with the use of HMG-CoA reductase, decreasing LDL cholesterol uptake due to the inhibition of the LDL-receptor expression as well as decreasing the bile cholesterol excretion. Moreover, in NAFLD the LDL and VLDL structure is changed such that they penetrate more easily the vascular walls. Altogether this leads to the atherogenesis increase which in NAFLD may result in the development of atherosclerotic plaques even in normal levels of total cholesterol and LDL. NAFLD also increases the thrombosis risk due to the increase of pool of proinflammatory cytokines, proatherogenic dyslipidemia, and hypercoagulation.

Some studies have also shown that in the settings of NAFLD the degree of left ventricular myocardial hypertrophy is markedly higher, atherosclerosis of the coronary and carotid arteries is more common, and the risk of ischemic heart disease is higher.

Thus, NAFLD is a confounding factor for cardiovascular diseases and requires a special approach to its treatment in such comorbid patients.

Drapkina O.M. NAFLD and cardiovascular comorbidity. In: *11th International Symposium of Gastroenterology, Saint Petersburg, Russia, 12–14 May 2016*. [online].
Available from URL: http://www.promedcs.eu/sites/default/files/abstractbook_2016.pdf

WHICH DOCTOR SHOULD TREAT NAFLD?

Rafael G. OGANOV

State Scientific Research Institute of Preventive Medicine, Moscow; Russian Federation

Non-alcoholic fatty liver disease (NAFLD) may be considered as an additional sixth criterion of metabolic syndrome (MS). At that, all manifestations of MS constitute a single pathogenesis underpinned by insulin resistance.

The MS manifestations include ischemic heart disease, arterial hypertension, type 2 diabetes mellitus, abdominal obesity, atherogenic dyslipidemia and NAFLD. Therefore, a patient with MS is a comorbid patient with a wide range of disease entities which are usually treated by different specialists: cardiologists, endocrinologists, gastroenterologists, dietitians and other specialists. However, in the real-life clinical settings the therapy prescribed to such a patient by different medical specialists does not often take into consideration presence of comorbid conditions constituting one pathogenesis. Moreover, sometimes prescriptions of different specialists may be contradictious or may be excessive which leads to polypragmasy and an additional medicinal load on the liver resulting in drug-induced hepatitis development.

In what way can we optimize the treatment approach to such comorbid patients with NAFLD, MS and concomitant conditions? One of the approaches is that the management of such a patient should be carried out by one physician who will be able to take into consideration all the comorbid conditions and prescribe the integrated treatment based on the total pathogenesis of MS manifestations.

In the current context this physician may be a general practitioner or a family therapist.

Oganov R.G. Which doctor should treat NAFLD? In: *11th International Symposium of Gastroenterology, Saint Petersburg, Russia, 12–14 May 2016*. [online].
Available from URL: http://www.promedcs.eu/sites/default/files/abstractbook_2016.pdf

ENDOSCOPIC SURGERY – EMERGING TECHNIQUES WHICH COMPLETELY CHANGED THE CURRENT CLINICAL PRACTICE

Julius SPICAK

Hepatogastroenterology, Institute for Clinical and Experimental Medicine, Prague; Czech Republic

The introduction of the fiberoptic gastroscope more than 50 years (Basil Hirschowitz) and papilosphincterotomy (L. Demling, M. Classen) more than 40 years ago were the landmarks changing the practice of gastroenterology fundamentally. Other breakthrough techniques involve polypectomy, stones removal, stenoses by-passing developed within the last two decades of the last century. Further refined techniques together with the accessories improvement enlarged the scale of therapeutic interventions considerably. ERCP has become almost exclusively a therapeutic procedure. The cannulation technique has changed in favour of primary guide wire insertion instead of contrast injection. In approximately 10% of cases the free cannulation is not achieved and precut technique has to be considered. Among various complications, pancreatitis represents both the most frequent and feared one. The preventive temporary pancreatic stent insertion and rectal administration of NSAIDs can reduce the risk of pancreatitis considerably. Dilation of benign strictures can be accomplished using a variety of dilating devices. Stenoses by-passing achieved primarily by the plastic stents insertion was further improved by the use of self-expanding metalic stents (SEMS). In bile duct obstruction, the stent insertion has to be properly planned in advance. Distal malignant obstruction is usually easy to by-pass, whereas hilar malignant obstruction represents a significantly greater challenge. The necessity to drain bilateral lobes is considered controversial, the failure to drain an opacified lobe will worsen the prognosis. In chronic pancreatitis, therapeutic endoscopy can be considered in three settings: drainage of the pancreatic duct by stents insertion or stones removal, pseudocyst drainage and treatment of biliary obstruction. Pancreatic fluid collection and pancreatic liquid necrosis can be drained using a transmural approach with placement of plastic or SEMS, and debris can be removed directly. The puncture has to be done using endoscopic ultrasound (EUS). SEMS are a major mode of palliative therapy in esophageal cancer and gastric outlet obstruction. Colorectal SEMS are useful adjunct to the palliative treatment of advanced malignancies. Currently a wide variety of interventional procedures are performed using EUS guidance including coeliac plexus neurolysis, drainage of fluid colections, drainage of biliary and pancreatic ducts and implementation of fiducial markers. POEM is a recently developed achalasia treatment method which combines the efficacy of surgical myotomy with the benefits of endoscopic procedures. Development of techniques of electrodissection and several accessories such as an oblique transparent cap has led to an increasing use of endoscopy treatment of Zenker's diverticulum. Barrett's esophagus as a complication of reflux esophagitis is a cause of the increased risk of esophageal adenocarcinoma. The patients with low grade dysplasia should be re-evaluated by the second opinion and in those with high grade dysplasia resection and thermal ablation seems to be the most reasonable therapy with recently emerging cryotherapy as the alternative. The advent of endoscopic resection techniques has enabled gastroenterologists to remove premalignant and early malignant lesions throughout the gastrointestinal tract. By the endoscopic dissection, the endoscopists can determine the incision line preoperatively and than resect even relatively large mucosal

tumors en bloc. Progress in endoscopy is nowadays evolutionary process continuously expanding in more and more areas covered in past by surgery only.

Spicak J. Endoscopic surgery – Emerging techniques which completely changed the current clinical practice. In: *11th International Symposium of Gastroenterology, Saint Petersburg, Russia, 12–14 May 2016*. [online]. Available from URL: http://www.promedcs.eu/sites/default/files/abstractbook_2016.pdf

11th International Symposium of GASTROENTEROLOGY
12–14 May 2016, Saint Petersburg, Russia

Endoscopic Surgery – Emerging Techniques which Completely Changed the Current Clinical Practice

Julius Špičák

IKEM
CZECH REPUBLIC

Endoscopy: Landmarks

Endoscopic Surgery – Definition, Principles

- Alternative of surgery by anatomic design/aims
- Disruption of the luminal integrity
- Adoption of new technologies (RFA, cryotherapy)
- Efficacy
- Recovery
- Costs
- Safety
- Aesthetic satisfaction

Endoscopic Surgery – Areas

- Bile duct obstruction
- Neoplastic lesions resection
- Chronic pancreatitis – duct obstruction
- Acute necrotizing pancreatitis
- GERD
- Achalasia
- Obesity

ERCP – Related Therapeutic Procedures

- Widespread
- Lot of centers harbor only less than 50 procedures
- Information only about peak of the iceberg
- Can be very smart, but potentially dangerous
- The only one procedure which can cause death even if done correctly
- Post-ERCP pancreatitis endoscopically irreversible
- Vague information about clinical success
- Vaguely defined quality/appropriatesess descriptors

ERCP Centers in the Czech Republic/Procedures 2015

N procedures	N centers
0–50	17
51–100	16
101–300	19
301–500	10
501–1,000	3
1,209	1
Total 11,998 / 6,345 PST	66

Conclusion: Significant proportion of the procedures are done in small volume centers.

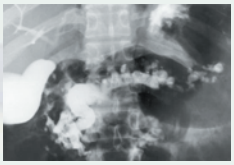
Recent achievements in ERCP: Pancreatitis Prevention by NSAIDs, Pancreatic Stent, Guide Wire Cannulation


Prophylaxis of post-ERCP pancreatitis:
European Society of Gastrointestinal Endoscopy (ESGE)
Guideline – Updated June 2014

ESGE

Chronic Painful Pancreatitis

- ESWL, Wirsungotomy, stones removal, intracorporeal lithotripsy, stricture by-passing
- Not standardized
- Highly selected patients in controlled studies
- Perspective when simple pathomorphology



Endoscopic or Surgical Intervention for Painful Obstructive Chronic Pancreatitis

- Metaanalysis
- Studies 3, surgery vs endoscopy 2, surgery vs conservative treatment 1

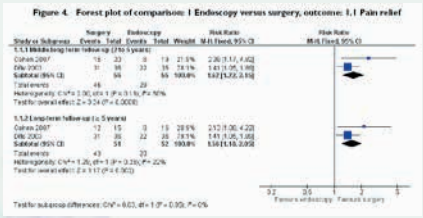


Figure 4 Forest plot of comparison: 1 Endoscopy versus surgery, outcome: 1.1 Pain relief

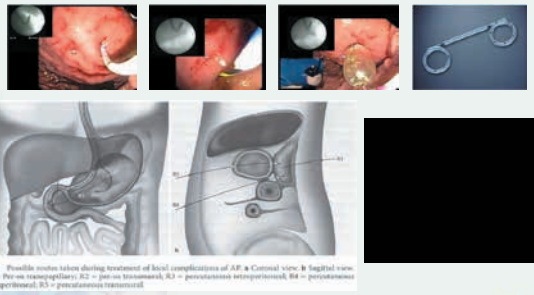
Conclusions: Surgery is superior to endoscopy in terms of pain relief.

Ali A., *et al.* Cochrane Collaboration 2015

Acute Necrotizing Pancreatitis

- Conservative treatment: Fluid replacement, nutrition, antibiotics
- Intervention – indications: Symptomatic pseudocysts, pancreatic fluid, **walled-of necrosis**, compartment syndrome, progressive deterioration
- Surgery: necrectomy: drainage, necrosis debridement
- Miniinvasive methods available: endoscopic transluminal, drainage under CT/sono, VARD, laparoscopy.
- 50% of all interventions
- Timing > 3 weeks
- Question: Could invasion reverse progressive deterioration

Transgastric Approach



Miniinvasive Techniques are not Identical

Techniques	Patients selection, patomorphology	Pros	Cons
Transluminal endoscopy	Organized collection	Good tolerance, definite solution	More sessions needed, complications 20%
Percutaneous CT directed	Tail, body collection	Relatively easy technique, the first step, even in diffuse necrosis	Pancreato-cut. fistulas, at 50% another invasion needed
Laparoscopy	Organized collection	Definite solution within 1 session, can be combined with CHE	Fistulas, difficult technique
Video assisted retroperit. necrectomy	Tail, body collection	Definite solution within 1 session	Lilited access to head
Dual techniques		Definite solution	More approaches – more complications
Step-up		Definite solution	More sessions – more complications

Transluminal Necrectomy – Metaanalysis

Author, year	N	Timing 1st. intervention	Endo 1st. Method	N sessions (mean)	Timing of necrectomy	Other techniques	Endoscopy alone %	Final success %	Mortality %	Complications /bleeding
Seewald, 2005	5	nr	100	15	nr	2 chir	60	60	0	3 (15)/2
Charnley, 2006	13	nr	0	5	0	2 chir 2 pc	69	69	15	2 (15)/nr
Voermans, 2007	25	144	100	2	4	2 chir	92	96	0	12 (48)/9
Papachristou, 2007	53	49	100	3	18	5 chir, 13 pc, 7 chir + pc	53	53	3	34 (64)/9
Escourrou, 2008	13	28	0	2	0	2 pc	85	85	0	10(77)/3
Schower, 2008	8	36	100	4	nr	2 surg	75	75	13	3 (38)/3
Coelho, 2008	56	35	100	5	nr	6 surg	88	88	4	6 (11)/2
Seifert, 2009	93	41	54	6	nr	12 surg, 1 transes.	86	81	8	27 (29) /13
Gardner, 2009	25	74	0	4	0	1 surg	96	88	0	8(32)/8
Gardner, 2011	104	46	100	4	nr	2 surg	96	91	7	38 (37)/21
Bakker. 2012	10	48	90	4	nr	2 durg	80	80	10	5 (50)/0
Bausch, 2012	18	78	0	Nr	0	7 surg, 1 pc	56	50	6	8 (44)/3
Abdelhafez, 2013	10	65	100	1	8	0	100	90	1	4 (40)/nr
Rische, 2013	22	nr	100	4	nr	3 surg	86	86	14	3 (13/nr

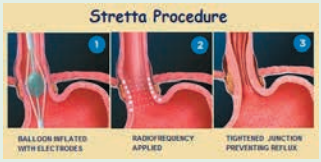
GERD

- PPI highly efficient
- Extraesophageal reflux less responsive to therapy
- Surgery: Nissen fundoplication
- Stretta, incisionless fundoplication

STRETTA – Safe and Effective

GERD Procedures	Anesthesia	Cost USD	No cases world	Years of experience	No centers	FDA averse events
Stretta	Concious sedation	2 000 – 3 500	15,000	13	125	29
EsophyX	General	7,000	11,000	7	200	2
Medigus	General	3,200	>100	2	2	0
Linx	General	12,000	1000	5	70	0

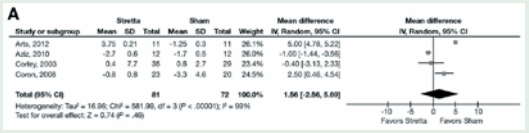
- Neurolysis or tissue necrosis
- Local inflammation
- Collagen deposition
- Muscular thickening of the LES
- Fewer transient relaxations

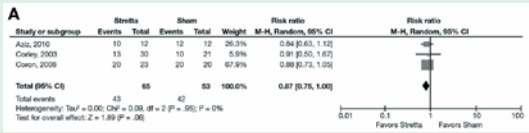


Jain D., *et al.* Clin Endosc 2016

No Evidence for Efficacy of Stretta?

- Metaanalysis
- Studies 4 (sham 3, PPI 1), patients 153

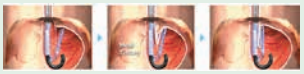




Conclusion: Stretta does nor provide significant changes in pH<4 (Figure 1), LESP, ability to stop PPI (Figure 2), and HRQOL

Lipka S., *et al.* Clin Gastroenterol Hepatol 2015

Transoral Incisionless Fundoplication for GERD



Review

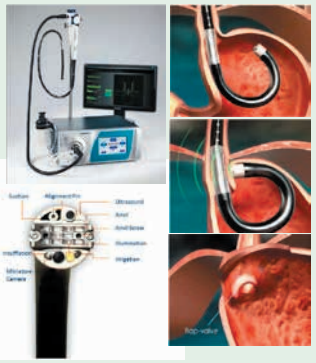
Author, year	N	Instrument	Controls	Clinical response	Endoscopic response	PPI requirement	Complications	Failure
Trad, 2014	40	EsophyX-2	PPI	6 m 65%	6 m 90%	0	0	0
Toomey, 2014	20	EsophyX-2	Toupet	92%	NR	NR	NR	NR
Wilson, 2014	100	EsophyX-2	–	HRQL 6 m 4	12 m 76%	6 m 20%	0	5
Cadière, 2008	86	EsophyX-2	–	HRQL 6 m 5	–	6 m 31%	Perforation 2	3
Rinsma, 2015	15	EsophyX-2	PPI	HRQL 8.5	6 m Impedance 2,294	NR	NR	0
Rinsma, 2014	15	EsophyX-2	–	HRQL 13.2	6m impedance 16.7	NR	0	NR
Testoni, 2015	50	EsophyX-2	–	QUAL 12 m 71	LES pressure 6 m 11	12 m 49%	Pneumothorax 2	4
Hunter, 2015	81	EsophyX-2	Sham	RDQ score 6 m 0.5	DeMeester 33.6 → 6 m 23.9	18 m 28%	0	2
Hakansson, 2015	44	EsophyX-2	Sham	QOLRAD 6 m 4.9 → 6.4	6 m Hill 1–2 80%	6 m 59%	0	

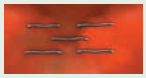
Jain D., *et al.* Clin Endosc 2016

How MUSE (Medigus Ultrasonic Surgical Endostapler (MUSE™) Works

Step by Step Overview:

1. Advance into stomach and retroflex
2. Retract MUSE system to 3 cm proximal to GE Junction, clamp tissue and staple fundus to esophagus
3. Remove MUSE to change stapling cartridge and repeat in 2–4 locations to create flap valve (150–180° anterior wrap)

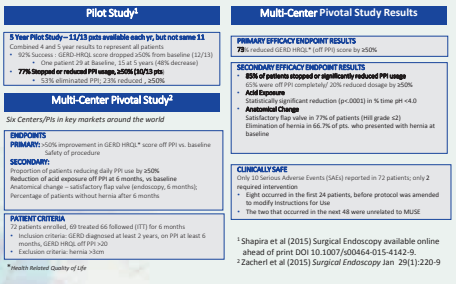




Each application fires 5 staples (quintuplet)

- Standard 4.8 mm titanium surgical staples
- Reliably used for gastroesophageal anastomosis for > 40 years

Summary of Clinical Data
MUSE Improves GERD-Related Quality of Life



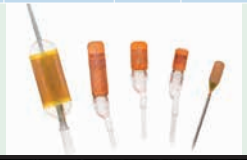
¹ Shapira et al (2015) Surgical Endoscopy available online ahead of print DOI 10.1007/s00464-015-4142-9.
² Zacherl et al (2015) *Surgical Endoscopy* Jan 29(1):220-9

Ablative Therapy for Barrett, Esophageal Dysplasia, Early Malignancy

Technique	Method	Frequency	Metaplasia eradication %	LGD eradication %	HGD eradication %	Complications %
RFA	High frequency current, topical destruction	2–3 m until resolution	54–97	80–100	81–90	2–6 (stricture, hemorrhagie)
PDT	O free radicals, topical destruction	1–2, ofteh followed ny Nd: Yag laser	52	93	77	30 (photosensitivity, stricture)
APC	Heat, topical destruction	8 weeks	0–55	–	76	15 (stricture)
Cryotherapy	Topical application, destruction	3–5 sessions	57–84	87	97	9 (stricture)

RFA

Author	Sessions, mean/median	Intest. Metaplasia complete eradication %	LGD complet eradication %	HGD complet eradication %	Rate of progression	Complications %
Ganz 2008	1	54.3	80.4	902.2		0.7
Fleischer 2008	1,5	97	–	–	–	0
Shaheen 2009	Up to 4	77.4	90.5	81.0	4	6.0
Fleisher 2010	3,4	92	–	–	–	0
Lyday	1.8–2.1	77	100	–	–	1.1



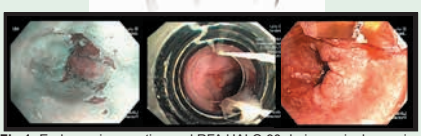


Fig.1: Endoscopic resection and RFA HALO 90 during a single session

RFA in IKEM I.

Baseline characteristics:	
No. of patients	73 (63 M, 10 F)
Age (range)	65 (22 – 87)
BORN:	
* Low-grade dysplasia	20 patients (27%)
* High-grade dysplasia	23 patients (32%)
* Early adenocarcinoma	30 patients (41%)

Treatment modalities:	
RFA as a single treatment modality	22 patients (30%)
RFA combined with endoscopic resection or dissection of a visible lesion	51 patients (70%)

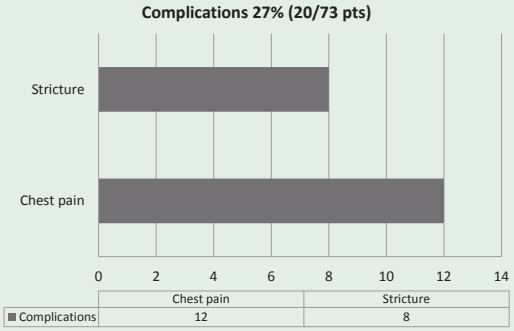
	HALO 360	HALO 90/60
RFA treatment sessions (n = 135)	38	97

RFA in IKEM II.

Complete remission of IM	68%
Complete remission of neoplasia	98.5%

Recurrences of IM	34%	75% normal neo-Z-line
		25% abnormal neo-Z-line
Recurrences of neoplasia	4% (3x LGD)	
Detection of buried glands	0%	

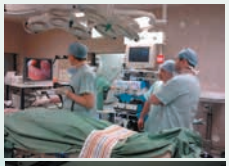
RFA in IKEM III.



Achalasia

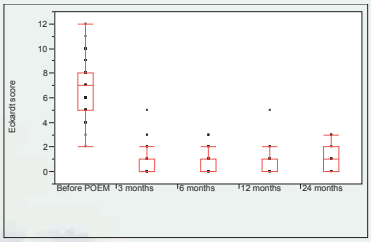
- No effect of medical treatment
- Dilation
- Laparoscopic Heller myotomy
- POEM

POEM in IKEM: Baseline Characteristics



Group of patients	123/120 POEM
M/F	59/43
Age (range)	47 (17–72)
Achalasia I, II, III	11/77/5
Jackhammer esoph.	1
Previous therapy	22 (22%) (3x LHM)

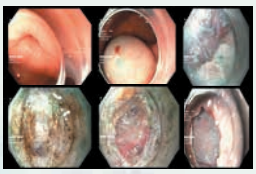
IKEM: Eckardt Score

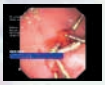


	Before POEM	3M	6M	12M	24M
Median	7	0*	0*	0*	1*
Variation range	3–12	0–5	0–3	0–2	0–3
IQ range	3	1	1	1	1

*p < 0,001

First Endoscopic Pyloromyotomy (G-POEM), Czech Rep. 9. 11. 2015





Endoscopic Submucosal Tunnel Dissection for Large Superficial Esophageal Squamous Cell Neoplasms

Table 1 Systematic literature review of endoscopic submucosal tunnel dissection for superficial esophageal squamous cell neoplasms n (%)

Ref.	Year	Lesions/cases	Mean size (mm)	Operation time (min)	En bloc resection	R0 resection	Complications	follow-up (mo)	Local recurrence
Linghu et al[28]	2011	11/11	48.2 (30-80)	78.6 (34-120)	100%	91.8%	Stenosis: 6 (54.5)	13.5 (3-30)	0%
Linghu et al[61]	2013								
Zhai et al[62]	2014								
Gao et al[63]	2012	17/17	24 (20-50)	128 (60-180)	100%	82.4%	Delayed bleeding: 1 (5.9)	NA	0%
Xiong et al[64]	2013	7/7	35.7 (20-40)	61 (37-110)	100%	100%	Immediate bleeding: 2 (28.6)	12	0%
Arantes et al[65]	2013	25/25	25 (10-60)	95 (60-210)	92%	84%	SE and ME: 2 (8) Perforation: 1 (4)	21.4 (3-36)	2 (8)
Fleche et al[67]	2013	11/11	45 (25-80)	76 (35-150)	100%	81.8%	SE: 9 (8.1%) Stenosis: 4 (36.4)	NA	1 (9.1)
Tan et al[66]	2014	1/1	50	NA	100%	100%	None	6	0%
Zhou et al[68]	2014	18/18	38 (45-74)	54.5 (32-85)	100%	100%	Immediate bleeding: 1 (5.6) SE: 1 (5.6) Stenosis: 3 (16.7)	6	0%
Total		90/88	37.8 (10-80)	83.3 (32-180)	88 (97.8)	77 (85.6)	Immediate bleeding: 4 (4.4) Delay bleeding: 1 (1.1) Perforation: 1 (1.1) SE or ME: 3 (3.3) Stenosis: 9 (10)	NA	3 (3.3)

Zhai Y.Q., *et al.* WJG 2016

Endoscopic Treatment for Gastrointestinal Stromal Tumor

Table 2 Recent publications reporting endoscopic enucleation and endoscopic full-thickness resection for upper gastrointestinal tumors originating from the proper muscle layer

Ref.	n	Method	Mean operation time (min)	Mean tumor diameter (mm)	Complete resection rate (%)	Complications/recurrence
Wang et al[60] (2014)	86	Standard ESD	-	-	100	4 delayed bleedings 9 perforations 5 local recurrences
Ye et al[57] (2014)	85	ESTD	57	19	100	4 pneumothorax and subcutaneous emphysema 2 pneumothorax 2 subcutaneous emphysema
Feng et al[46] (2014)	48	EFTR	60	16	100	0
Li et al[44] (2012)	143	ESD (134), EFTR (6), ESTD (3)	45	18	94[1]	2 pneumothorax, 1 subcutaneous emphysema
Bialek et al[52] (2012)	22	Standard ESD	-	-	68[1]	2 perforations
Lin et al[58] (2013)	31	EMD	77	22	97	4 perforations
Inoue et al[59] (2012)	7	OET	152	19	100	0
Geng et al[61] (2012)	12	ESTD	48	20	83	2 pneumothorax and subcutaneous emphysema
Zhou et al[62] (2011)	26	EFTR	105	28	100	0
Hwang et al[63] (2009)	25	ESD	-	29	64	3 perforations
Lee et al[64] (2006)	11	ESD	61	21	75	0

Kim H.H., *et al.* WJGE 2015

Endoscopic Full-Thickness Resection for Gastric Tumor

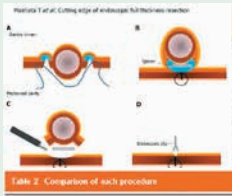


Table 1 Representative publications reporting endoscopic full-thickness resection for upper gastrointestinal tumors

Ref.	n	Mean operation time (min)	Mean tumor diameter (mm)	Complete resection rate (%)	Complication rate (%)
Zhou et al[28]	26	105	28	100	0
Feng et al[29]	48	60	16	100	0
Hoang et al[30]	35	90	28	100	0
Schmidt et al[31]	31	60	20.5	90.3	9.7 (perforation)
Guo et al[32]	25	40.5	12.1	100	0

Table 2 Comparison of each procedure

	Instruments	Indication for EGC	Retrieval route	Intestinal gastric perforation	Advantage	Limitation
EFTR	Endoscopy only	No	Transoral	Required	Simple methods using intraluminal endoscopy only	Risk of contamination, endoscopic skills required
Classical LECS	Endoscopy + Laparoscopy	No	Transabdominal	Required	Accurate to determine the resection line, laparoscopic assistance	Risk of contamination, Risk of contact to tumor surface
Inverted LECS	Endoscopy + Laparoscopy	Indicable	Transoral	Required	Accurate to determine the resection line, laparoscopic assistance	Risk of contact to cancer surface, tumor size
CLEAN-NET	Endoscopy + Laparoscopy	Yes	Transabdominal	Not required	No transluminal communication	Excessive resection of the mucosa, difficult to determine the resection line
NEWS	Endoscopy + laparoscopy	Yes	Transoral	Not required	Accurate to determine the resection line, laparoscopic assistance, no transluminal communication	Tumor size, experience required, time-consuming

Endoscopic Therapy for Weight Loss: Alternative or Bridge to Surgery

- **Advantage: Reversible, safer, less invasive, brudge between medical treatment and surgery**

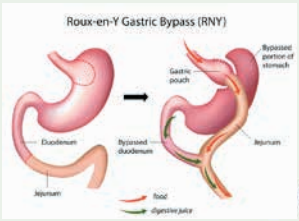
- *Restrictive procedures*
- Incisionless Operating Platform
- OverStich sleeve gastroplasty
- EndoCinch
- TransOral GAstroplasty
- ACE stapler
- Transoral Endoscopic Restrictive Implant System

- *Bypass procedures*
- EndoBarrieer

- *Space-occupying device*
- Orbera balloon
- Heliosphere BAG
- Reshape Duo balloon
- Abalon balloon
- Transpyloric shuttle
- SatiSphere

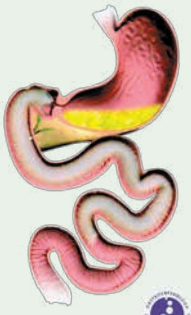
- *Aspiration therapy*
- AspireAssist

- *Endoscopic revision of gastric bypass*

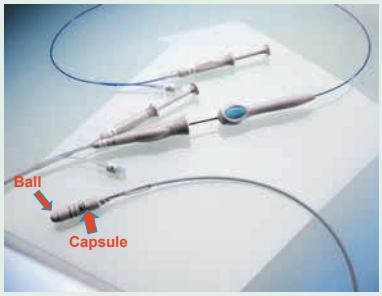


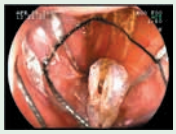
EndoBarrier® Concept

- Implantation/ Explantation by Endoscop
- Copy the Effect of a surgical Bypass Roux-en-Y
- Prohibit contact of food between duodenum / proximal Jejunum 60 cm

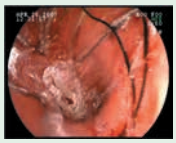


EndoBarrier ® Implantation System



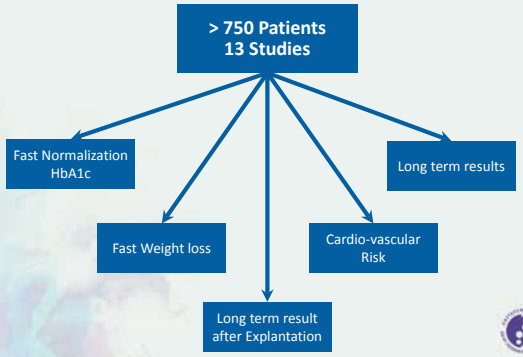


Sleeve bunching within anchor



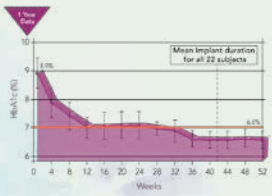
Sleeve bunching resolved

Clinical Experience



Clinical Results – 12 Months

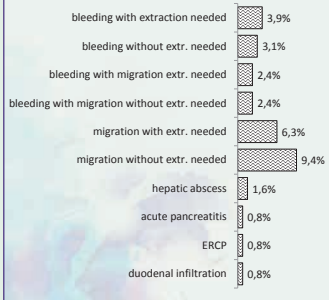
Reduction in HbA1c

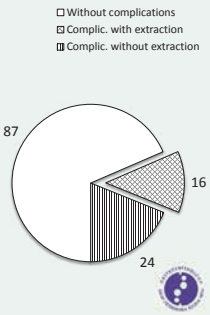


EndoBarrier Program in IKEM

- Start of the program – 8/2013
- 127 treatments till now
- Institute of Clinical and Experimental Medicine – Prague
- Complex Multidisciplinary Team Global %EWL – **32**
- HbA1c minus **1.8** mmol/mol
- Complications rate: 30%, extraction of EB needed 12%
- Surgery 1
- No death

EndoBarrier Program in IKEM





Endoscopic Sleeve

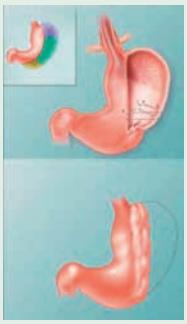
Single-center case series n=147

Primary Obesity Surgery Endolumenal (POSE(™)); plications or 2 parallel plications st the anterior and posterior site of the stomach

Results: no severe complications mean procedure time: 75 min. and 2,5h

Initial BMI 38

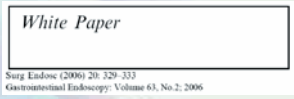
Total weight loss (TWL), percentage of TWL (%TWL), percentage of excess weight loss (%EWL) **TWL of 16.6 ± 9.7 kg, %TWL of 15.1 ± 7.8, and %EWL of 44.9 ± 24.4**



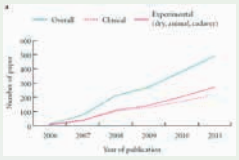
Lopez-Nava et al. Endoscopy 2014; 46: 449–452
Sharaiha et al. Endoscopy 2015; 47: 164–166

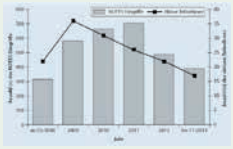
NOTES

- White paper 2005
- Transvaginal: Cholecystectomy, splenectomy, liver biopsy/resection, sigmoidectomy, nephrectomy, peritoneoscopy, sleeve gastrectomy, appendicetomy,
- Transgastric: Cholecystectony, peritoneoscopy, appendicetomy,
- Transvesical: Peritoneoscopy


White Paper
Surg Endosc (2006) 20: 329–333
Gastrointestinal Endoscopy: Volume 63, No.2: 2006

NOTES in Germany





- 2008–2013
- N 2,992
- Hybrid transvaginal cholecystectomy 88.7%
- Hybrid transvaginal/transgastric appendectomy 6.1%
- Hybrid transvaginal/transrectal colon procedures 5.1%
- Complications 3.7%
- Conversion 1.5%

Lehmann KS et al. Chirurg 2015

Transvaginal Hybrid NOTES vs. Needlescopic CHE

RCT

Outcomes	Transvaginal	Needlescopic
N	20	20
Aesthetic satisfaction, 3m, 1–5, mean	1.00	1.35*
Overall satisfaction	1.2	1.3
Cummulative abdominal pain	8 (4–16)	14.0 (8–19)
Incisional hernia	0	0
Aesthetic satisfaction, 6m, 1–5, mean	1.00	1.7*
Overall satisfaction	1.15	1.25*
Abdominal pain	0	0
Incisional hernie	0	0

Conclusions: Both method comparable in safety, TVC caused less pain, increased satisfaction

Bulian DR et al. Langenbecks Arch Surg 2014

Transvaginal Hybrid NOTES CHE

Review; transvaginal vs laparoscopy

Studies 14

Patients	TVG 530 %	LP 615 %
Postoperative complications	5.6	7.5
Bile duct injury	0.6	0.4
Operative time WMD	+ 14.81	
Time to normal activities	2–6.4	4–14.4

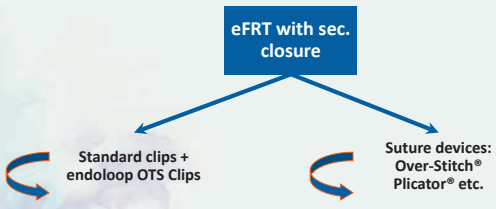
Lehmann KS et al. Chirurg 2015

Endoscopic Surgery – Conclusion

- Therapeutic endoscopy is changing considerably covering more and more space
- Nobody can master all endoscopic techniques
- Highly sophisticated technology has to be proved in RCT
- Better organization desirable
- Future – new technologies, robotization

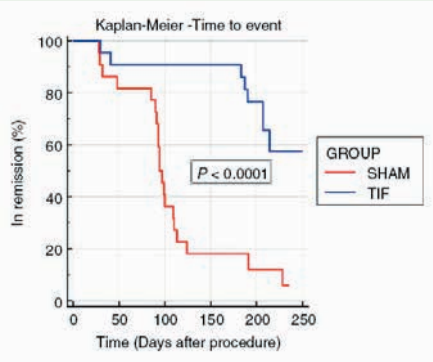
Endosc. Full Thickness Resection

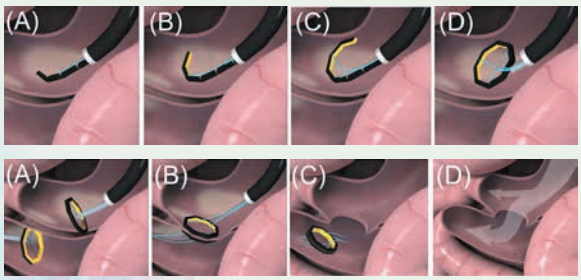
eFTR = endoscopic full thickness resection
→ defect of the wall → closure with / without laparoscopic assistance

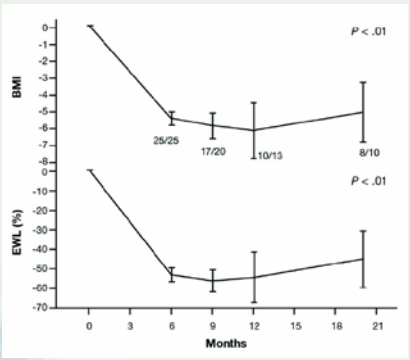


Tumors ≤ 2 cm

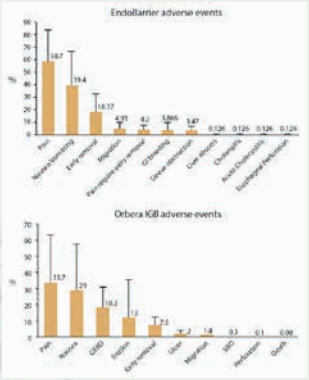
Endoscopic Sleeve Gastroplasty

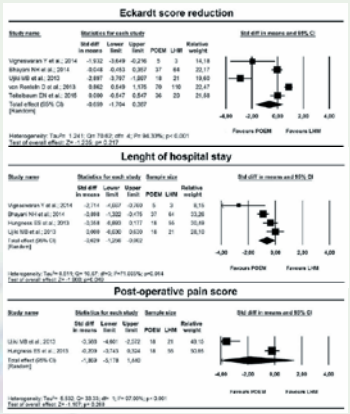






Endoscopic Bariatric Therapies – Complications – Balloon vs. EndoBarrier





THE EUROPEAN PERSPECTIVE OF ENDOSCOPIC SUBMUCOSAL DISSECTION

Ondrej URBAN

Gastroenterology dept., Hospital Vitkovice, Ostrava-Vitkovice; Czech Republic

Background
Endoscopic submucosal dissection (ESD) has been developed in Japan as the method for *en block* resection of gastrointestinal cancers with very low risk of lymph node metastasis. In such cases, ESD provides similar oncological results and, at the same time, avoids risks of surgery.

Gastric ESD (G-ESD)
In 2016, indications for G-ESD are as follows:

A) *Guideline*
- Elevated type (0–IIa) cancer ≤ 20 mm in diameter;
- Depressed type (0–IIc) cancer ≤ 10 mm;

+ all such lesions should be moderately or well-differentiated, with no ulceration, confined to the mucosa and have no lymphatic or vascular involvement histologically.

B) *Expanded*
- Intramucosal, well-differentiated adenocarcinoma, without ulceration regardless of lesion size;
- Intramucosal, well-differentiated adenocarcinoma, with ulceration, ≤ 30 mm in diameter;
- Superficially (sm1) invasive, well-differentiated adenocarcinoma, ≤ 30 mm in diameter.

Results of G-ESD:
Toyonaga et al. reported results of G-ESD performed on 2 038 Japanese patients during 2002–2012. *En block* and R0 resection was achieved in 2 027 (99.5%) and 1 984 (97.4%) of cases respectively. In another Japanese series of 3 778 G-ESD with 5 year follow up, 0 patients in guideline group and 3 (1.15%) in expanded criteria group developed metastasis. In Europe, *Nunes et al.* reported *en block* and R0 resection in 94% and 91% respectively with longterm curative results in 86%. The risk of perforation is 1.2–5.2%.

Esophageal ESD (E-ESD)
In 2016, indications for E-ESD of squamous cell carcinoma (SCC) are as follows:

A) *Absolute*
- SCC limited to epithelium or lamina propria (m1, m2);

B) *Relative*
- SCC involving muscularis propria (m3) or superficial submucosa (sm1).

Results of E-ESD:
Toyonaga et al. reported results of E-ESD performed on 559 Japanese patients during 2002– 2012. *En block* and R0 resection was achieved in 557 (99.6%) and 547 (97.9%) of cases respectively.

Colorectal ESD (CR-ESD)

In 2016, indications for colorectal ESD (CR-ESD) are as follows:

- Lesions for which *en block* resection is required but difficult to achieve by EMR, including
  – LST-NG, particularly LST-NGPD;
  – lesions showing a Vi pit pattern;
  – carcinomas with shallow T1 (sm) invasion;
  – large depressed-type tumors and large protruded – type lesions suspected to be carcinoma;
- Mucosal tumours with submucosal fibrosis;
- Sporadic localized tumours in conditions of chronic inflammation such as ulcerative colitis;
- Local residual or recurrent early carcinomas after endoscopic resection.

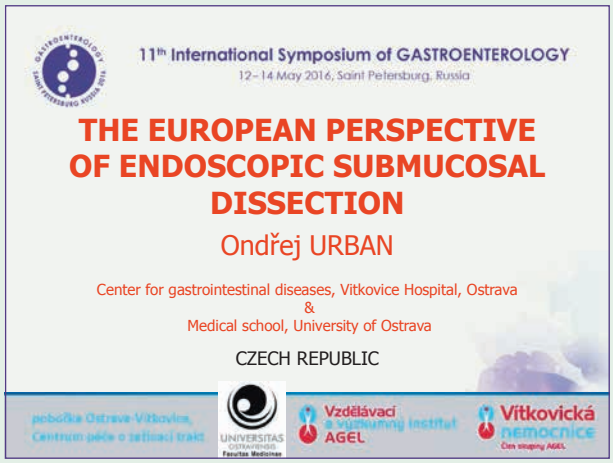
Toyonaga et al. reported results of CR-ESD performed on 1 143 Japanese patients during 2002–2012. *En block* and R0 resection was achieved in 1 135 (99.3%) and 1 128 (98.7%) of cases respectively. The risk of perforation in studies is 1.1–3.8%.

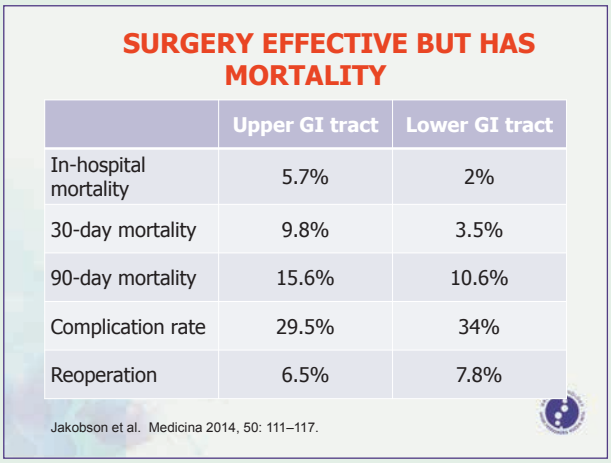
European perspective of ESD

Compared to Asia, incidence of both SCC and EGC in Europe is low. Nevertheless, the indications for E-ESD and G-ESD are straightforward due to the risks of surgery and lower quality of life after surgical resection. CR-ESD spreads rapidly, but it is wise to keep in mind, that most of colorectal lesions can be treated safely by piecemeal EMR and both the risks and impact on quality of life of colorectal surgery are lower than in the cases of foregut tumors. To further improve results of ESD in Europe, training involving animal models work and participation on workshops with ESD experts are advocated. For further reading, recently launched ESGE guideline is available.

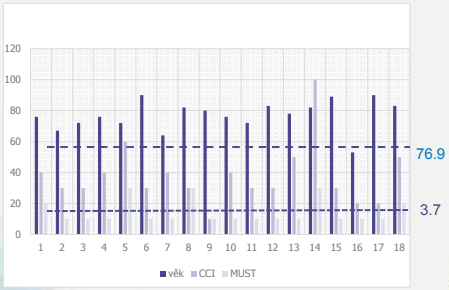
ondrej.urban@nemvitkovice.cz

Urban O. The European perspective of endoscopic submucosal dissection. In: *11th International Symposium of Gastroenterology, Saint Petersburg, Russia, 12–14 May 2016*. [online].
Available from URL: http://www.promedcs.eu/sites/default/files/abstractbook_2016.pdf



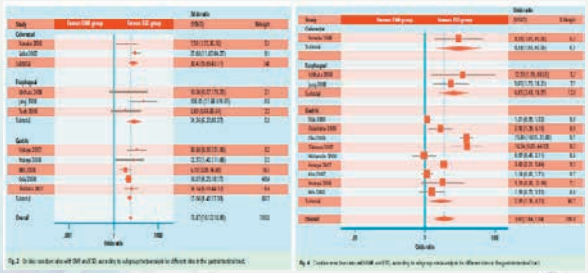


RISK PROFILE OF PATIENTS TREATED BY G-ESD (N=18)



Urban O, Unpublished data.

ESD SUPERIOR TO EMR (EN BLOC, R0, CURATIVE)



Lian J., GIE 2012; Park Y-M., Surg Endosc 2011; Cao Y., Endoscopy 2009

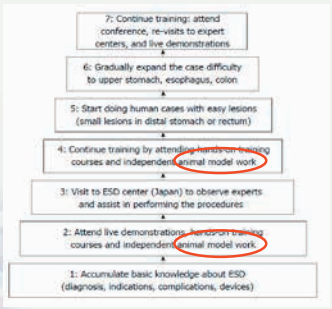
WHOM TO TRAIN ?

JAPAN:

- Knowledge as primary physicians
- An average level of endsocopic skills
- Wanting to acquire the sufficient knowledge and competent skills for ESD
- Not every endoscopist can became a preceptee of ESD

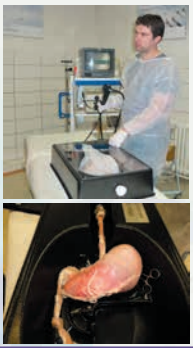
Fujishiro M., *et al.* Dig Endosc 2012; S1: 121–123.

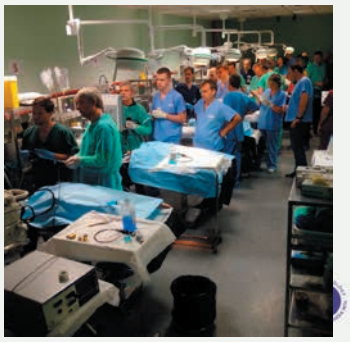
PROPOSED TRAINING ALGORITHM FOR WESTERN PHYSICIANS



Coman RM, Gotoda T, Draganov PV. World journal of gastrointestinal endoscopy 2013,5(8): 369–378.

COMPACT ERLANGEN SIMULATOR (EASIE) & LIVE PORCINE MODEL HANDS-ON TRAINING





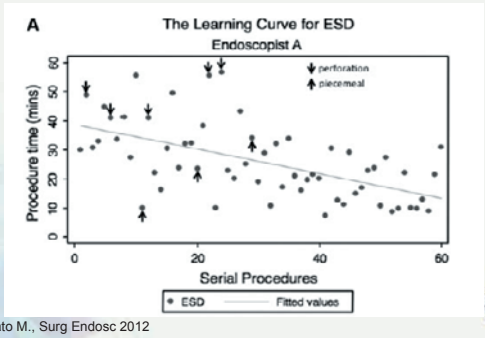
TRAINING IS EFFECTIVE

30 ESD (8 ex vivo, 22 in vivo)
First vs second half of gastric cases
98.9 ± 62.4 min vs 61.7 ± 17.6 min, p = 0.04

CONCLUSION: Training in animal models could help endoscopists overcome the learning curve before starting ESD in humans.

Parra-Blanco A., *et al.* World J. Gastroenterol 2010; 16: 2895–900.

TIME VS PERFORATION, PIECEMEAL



Kato M., Surg Endosc 2012

WHO IS COMPETENT FOR ESD IN JAPAN?

G-ESD	CR-ESD
30 supervised cases	80 cases
Guideline lesion in < 2 h	< 15 min/cm^2
Curative resection rate > 90%	En bloc > 95%
Complication rate < 3%	R0 > 90%
	Perforation < 6%

Fujishiro M., *et al.* Dig Endosc 2012; 24(S1): 121–123

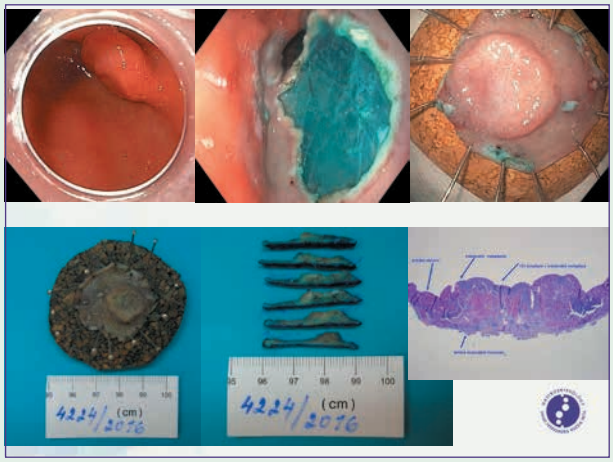
INSTITUTIONAL REQUIREMENTS

ESGE guidelines
Written policy for perforation management
Discussion of cases in tumor boards
Regular gastro- pathological meetings

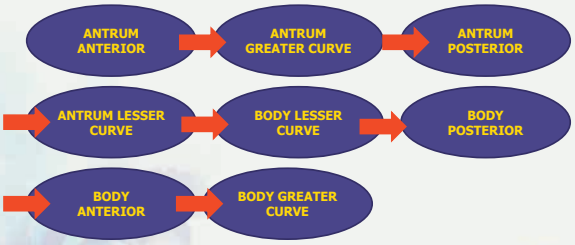
No consensus about minimal case load vs. imperative to perform > 10–25 cases/year

Pimentel-Nunes, *et al.* ESD: ESGE guideline, Endoscopy 2015; 47: 829–854
Paspatis Gregorios A., *et al.* ESGE position statement, Endoscopy 2014; 46: 693–711
Deprez P.H., *et al.* Endoscopy 2010; 42: 121–124.

TECHNOLOGY LIMITATIONS IN EU



DIFFICULTY OF GASTRIC ESD

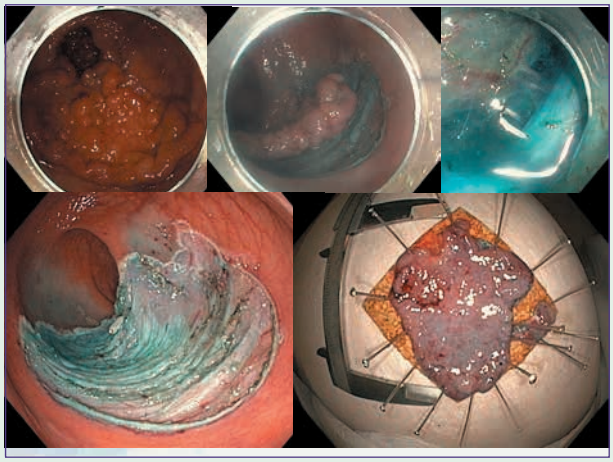


JAPANESE VS. EUROPEAN EXPERIENCE WITH G-ESD

- *Tokyo area (Hoteya S, Japan-Korean joint symposium 2012)*
  2005–2009: 5,777 lesions
  R0 94.1%, 1.2%, Local rec. 0.3%, Dist. meta 0.16%
- *Portugal (Nunes PP, Endoscopy 2014)*
  2003–2013: 195 lesions , 141 ESD
  En bloc 94%, R0 91%, Perf. 2%, Bleeding 8%
- *Czech Rep. (Urban O, UEGW 2015)*
  2011–2014: 25 lesions
  En bloc 85%, R0 85%, Perf. 8%, Bleeding 0%

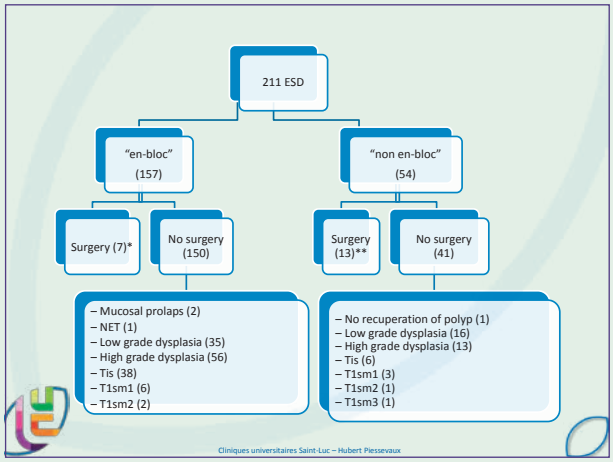
CR-ESD: THINGS TO BE CONSIDERED FIRST !

- EMR effective for lesions < 20 m
- Virtually 0 risk of sm invasion for LST-GH of any size
- Local residual/reccurent neoplasia endoscopicaly treatable in 91% during one session
- Surgery in colon less invasive, functional results good
- Rectal cancers technically easier, biologicaly worse



JAPANESE VS. EUROPEAN EXPERIENCE WITH CR-ESD

- *Japan (Toyonaga T, Clinc Endosc 2012)*
  2002–2012: 1,143 lesions
  En bloc 99.3% R0 97.8% Perf. 1.5%
- *France (Rahmi G, Endoscopy 2014)*
  2010–2012: 45 lesions (all rectal)
  En bloc 64%, R0 53 %, Perf. 18%
- *Czech Rep. (Urban O, UEGW 2015)*
  2011–2014: 43 lesions (post EMR recurrence 9)
  En bloc 69.8%, R0 55.8%, Perf. 12%



BARRETT OESOPHAGUS RELATED NEOPLASIA

ESD has not been shown to be superior to EMR for excision of mucosal cancer and for that reason EMR should be preferred.

ESD may be considered in selected cases, such as lesions larger than 15 mm, poorly lifting tumors, and lesions at risk for submucosal invasion.

Pimentel-Nunes, *et al.* ESD: ESGE guideline, Endoscopy 2015; 47: 829–854.

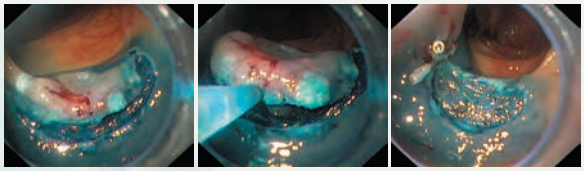
PROSPECTS: TRACTION, CUTTING, LIFTING…

PTA-EMR *(Takumo1997)*
Magnetic anchor system *(Gotoda 2009)*
External grasping forceps *(Imaeda 2006)*
Peroral traction assisted ESD *(Jeon 2009)*
Spring device *(Sukurazawa 2009)*
Clip–band techniqe *(Parra-Blanco 2011)*
Medical–ring assisted ESD*(Matsumoto 2012)*
Endolifter

Scissors-type devices (Clutch cutter, SB knife, FD-Y0005)

Gel for SM injection *(Saxena 2014)*

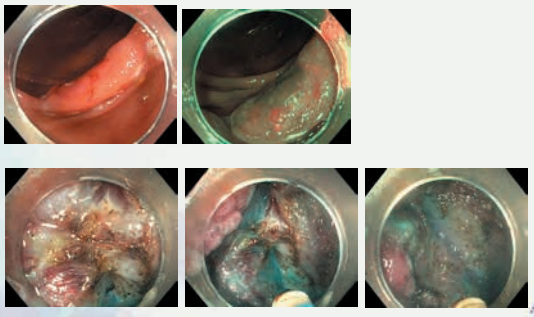
SIMPLIFIED (S-ESD)



OUTCOMES OF S-ESD VS. ESD

Author	Method	n	Size (mm)	Time (s)	En bloc %	Perfor. %	Delayed bleed %
Yoshida	S-ESD	22	21.2 (10–40)	57 (18–85)	77.3	4.5	4.5
	ESD	166	31.2 (12–130)	94 (100–420)	92.2	3.8	2.5
Oka	S-ESD	36	20–NR	NR	100	5.6	NR
	ESD	95	20-NR	NR	NR	1.1	NR
Toyonaga	S-ESD	44	17 (4–33)	27 (8–98)	90.9	4.5	2.3
	ESD	468	30 (6–158)	60 (11–335)	98.9	1.5	1.5

POCKET-CREATION METHOD, MUSCLE RETRACTING SIGN



Hayashi Y., Yamamoto H., *et al.* Endoscopy 2014

ENDOSCOPIC FULL THICKNESS RESECTION (EFTR)

Wall resect study (n = 79)

- Adenoma with non-lifting (53%)
  T1 ca (14%)
  Adenoma involving appendix (19%)
  Submucosal tumor (12%)
- Technical success (en bloc) 86%, (R0) 78%
- Procedure time 11 (1–90min)
- Adverse event 5.1%
- Residual adenoma after 3 month (n = 15) 0%

Schmidt T., *et al.* OP054-LB3, UEGW 2015.

CONCLUSIONS: ESD IN EUROPE

– has changed paradigm of early GI tract cancer treatment
– compared to country of its origin is performed in different clinical scenario
– should be started after relevant training
– is mostly needed for colorectal lesions
– is still technically developing

EUS-GUIDED AND EUS-ASSISTED INTERVENTIONAL BILIARY ENDOSCOPY AND ENDOSCOPIC ANASTOMOSES

Rastislav KUNDA

Department of Surgical Gastroenterology L, Aarhus University Hospital, Aarhus; Denmark

Endoscopic ultrasound (EUS) has established its role in diagnostics since early 1980s, with significant improvement of ultrasound imaging, endoscopic imaging as well as various tissue acquistion techniques. Therapeutic EUS has been rather limited and mostly applied only in celiac plexus neurolysis and drainage of pseudocysts and peripancreatic fluid collections. These procedures have been performed with accessories developed mainly for diagnostic EUS as well as endoscopic retrograde cholangiopancreaticography (ERCP). Thus development of new dedicated instruments and accessories was required.

Over the last 5 years, with development and introduction of such specific tools, therapeutic interventional EUS (iEUS) started its massive outbreak. Novel and dedicated instruments and devices help to reinvent treatment of pancreatic and peripancreatic fluid collections, facilitate gaining access to the bile duct in case of failed ERCP or percutaneous transhepatic biliary drainage (PTCD), allows creation of anastomoses on both intrahepatic and extrahepatic bile ducts, pancreatic duct as well as in between various parts of upper gastrointestinal tract.

EUS-assisted or EUS-guided approach is applied both in malignant and benign cases, especially in order to create effective drainage from bile ducts, occluded by tumors or even by stone disease. Such approach is extremely helpful in gaining biliary access also in cases of difficult anatomy, especially in surgically altered anatomy (i.e. gastric bypass, Roux Y anastomoses, etc.), where standard ERCP is not an option.

EUS-guided choledochoduodenostomy, EUS-guided hepaticoduodenostomy, EUS-guided hepaticogastrostomy, EUS-guided cholecystogastrostomy and EUS-guided cholecystoduodenostomy are supplementary to standard ERCP as well as to EUS-assisted procedures on bile ducts. Aarhus University Hospital is leading in pioneering center in clinical application of all these techniques. They are fully implemented within therapeutic algorithms of both malignant and benign patient in order to facilitate fast track clinical approach. Procedures are complementary to other standard techniques and performed on regular basis. Appropriate technique is chosen based on underlying pathology, anatomic site of bile duct occlusion, diameter of bile ducts, etc. Some of procedures are even performed routinely on outpatient basis and does not require general anesthesia. High volume of these procedure is result of tight multidisciplinary approach and multidisciplinary decision making, with main target to provide as fast as possible treatment for patients with the highest possible quality of care. Therapeutic tools and accessories are continuously improved in order to expand field of indications as well as to achieve the highest possible technical and clinical success rates, respectively.

Kunda R. EUS-guided and EUS-assisted interventional biliary endoscopy and endoscopic anastomoses. In: *11th International Symposium of Gastroenterology, Saint Petersburg, Russia, 12–14 May 2016*. [online]. Available from URL: http://www.promedcs.eu/sites/default/files/abstractbook_2016.pdf

ENDOSCOPIC DIAGNOSIS AND TISSUE SAMPLING IN BARRETT'S OESOPHAGUS

Eduard VESELINY

1st Department of Internal Medicine, Faculty of Medicine, Pavol Jozef Safarik University in Kosice; Slovakia

The diagnosis of GERD is associated with a 10–15% risk of Barrett's esophagus (BE), a change of the normal squamous epithelium of the distal esophagus to a columnar-lined intestinal metaplasia (IM). Endoscopy assessment and tissue acquisition are fundamental for correct diagnosis and management of BE. The proper collection of tissue specimens is required for accurate pathologic diagnosis. Communication between endoscopist and pathologist facilitates effective tissue collection and analysis.

BE should be diagnosed when there is extension of salmon colored mucosa into the tubular esophagus extending ≥ 1 cm proximal to the gastroesophageal junction (GEJ) with biopsy confirmation of IM. The yield for IM correlates directly with the number of endoscopic biopsies obtained. Endoscopic biopsy should not be performed in the presence of a normal Z line or a Z line with < 1 cm of variability. IM of cardia is very common, being described in up to 20% of asymptomatic subjects presenting for routine open access endoscopic examinations. Studies have suggested that IM of the cardia is not more common in BE patients compared with controls, and that the natural history of IM at the EGJ is associated with *Helicobacter pylori* infection and not associated with esophageal adenocarcinoma (EAC). Based on this information, biopsy of a normal or slightly irregular EGJ is not recommended. In the presence of BE, the endoscopist should describe the extent of metaplastic change including circumferential and maximal segment length using the Prague classification. The location of the EGJ has been defined as the anatomic region where the distal extent of the tubular esophagus is in contact with the proximal extent of the gastric folds. The location of the proximal extent of the gastric folds can be affected by respiration, air insufflation during endoscopy, and esophageal and gastric motility. The location of the diaphragmatic hiatus, GEJ, and squamocolumnar junction should be reported in the endoscopy report.

In patients with suspected BE, at least 8 random biopsies should be obtained to maximize the yield of IM on histology. In patients with short (1–2 cm) segments of suspected BE in whom 8 biopsies may be unobtainable, at least 4 biopsies per cm of circumferential BE, and one biopsy per cm in tongues of BE, should be obtained.

Unsedated transnasal endoscopy (uTNE) can be considered as an alternative to conventional upper endoscopy for BE screening (strong recommendation, low level of evidence). If initial endoscopic evaluation is negative for BE, repeating endoscopic evaluation for the presence of BE is not recommended. If endoscopy reveals esophagitis, repeat endoscopic assessment after PPI therapy for 8–12 weeks is recommended to ensure healing of esophagitis and exclude the presence of underlying BE. Surveillance should be performed with high-definition/high-resolution white light endoscopy. Routine use of advanced imaging techniques other than electronic chromoendoscopy is not recommended for endoscopic surveillance at this time. Endoscopic surveillance should employ four-quadrant biopsies at 2 cm intervals in patients without dysplasia and 1 cm intervals in patients with prior dysplasia. Mucosal abnormalities should be sampled separately, preferably with endoscopic mucosal resection.

Inability to perform endoscopic mucosal resection in the setting of BE with nodularity should lead to consideration to referral to a tertiary care center. Biopsies should not be obtained in mucosal areas with endoscopic evidence of erosive esophagitis until after intensification of antireflux therapy to induce mucosal healing. For BE patients with dysplasia of any grade, review by two pathologists, at least one of whom has specialized expertise in GI pathology, is warranted because of interobserver variability in the interpretation of dysplasia.

Veseliny E. Endoscopic diagnosis and tissue sampling in Barrett's oesophagus. In: *11th International Symposium of Gastroenterology, Saint Petersburg, Russia, 12–14 May 2016*. [online].
Available from URL: http://www.promedcs.eu/sites/default/files/abstractbook_2016.pdf

11th International Symposium of GASTROENTEROLOGY
12–14 May 2016, Saint Petersburg, Russia

ENDOSCOPIC DIAGNOSIS AND TISSUE SAMPLING IN BARRETT'S ESOPHAGUS

Eduard VESELINY

1st Dpt. of Internal Medicine, Faculty of Medicine, P. J. Šafárik University in Košice

SLOVAKIA

Introduction

- GI endoscopy and tissue acquisition are fundamental
  - **diagnosis** and **management** of BE
- The proper collection of tissue specimens is required for accurate pathologic diagnosis (BE ± IM or GM, IGD, LGD, HGD, IMC, EAC)
- Communication between endoscopist and pathologist facilitates effective tissue collection and analysis

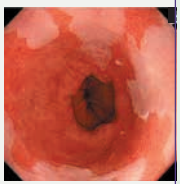
Endoscopic diagnosis of BE

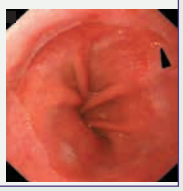
- Transoral EGD is still the gold standard dg tool for BE
- Unsedated transnasal endoscopy (uTNE)
  - Comparable rates of NDBE detection
    Jobe BA, Am J Gastroenterol 2006
    Shariff MK, GIE 2012
  - Can be considered as an alternative for BE **screening**
    ACG guidelines, AJG 2015
  - But more problematic tissue sampling (large capacity forceps are better)
- ➢ **Not recommended** in routine BE **surveillance**

BSG guidelines, Gut 2014
ASGE guidelines, GIE 2012

Endoscopic diagnosis of BE

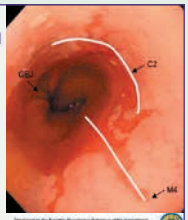
- ➢ **"**Columnar epithelium should be clearly visible endoscopically above the GEJ**"** (> 1 cm)
- ➢ Assess landmarks:
  - Diaphragmatic hiatal pinch
  - **GEJ** – the proximal limit of the longitudinal gastric folds with minimal air insufflation
  - **SCJ**
- ➢ Distinguish from an **irregular Z-line**
  - tongues of columnar-lined epithelium shorter **< 1 cm**
  - biopsies generally not recommended
  - If, denote as … **"biopsies from GEJ"** (not BE)





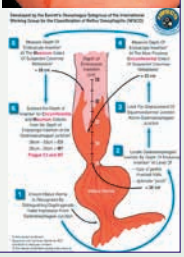
ACG guidelines, ACG 2015
BSG guidelines, Gut 2014

The Prague C&M classification



- Consensus-driven, explicit criteria
- Validated and reproduced in a different populations

Sharma P, Gastroenterology 2006
Lee YC, Endoscopy 2010
Vahabzadeh B, GIE 2012



➢ **Record the length**
(C- and M- extent of columnar-lined esophagus in cm)
- All three landmarks (diaphr. hiatus, EGJ, SCJ) should be mentioned in report
- + any separate islands above it (often after ablation th)

ACG guidelines, ACG 2015
BSG guidelines, Gut 2014

Minimum endoscopic dataset required in BE

Finding	Reporting system	Nomenclature
Barrett's oesophagus length	Prague classification	CnMn (where n is length in cm)
Barrett's islands	Describe distance from the incisors and length in cm	Descriptive in the text
Hiatus hernia	Distance between diaphragmatic pinch and GOJ	yes/no; cm
Visible lesions	Number and distance from incisors	yes/no; cm
Classification of visible lesions	Paris classification	0-Ip, protruded pedunculated 0-Is, protruded sessile 0-IIa, superficial elevated 0-IIb, flat 0-IIc, superficial depressed 0-III, excavated
Biopsies	Location and number of samples taken	n cm (distance from incisors) Xn

GOJ, gastro-oesophageal junction

BSG guidelines, Gut 2014

Biopsy protocol and site mapping
(diagnosis or surveillance of BE)

The Seattle biopsy protocol:

- Targeted biopsies on visible lesions
- Four-quadrant random biopsies every 2 cm /1cm in dysplasia/
- Safe, recommended, but time consuming
- Only limited adherence to the protocol (10–79%)
  - Poorer for longer segments
  - In failure.. significantly lower rate of dysplasia detection

Das D, Am J Gastroenterol 2008
Abrams JA, Clin Gastroenterol Hepatol 2009

- Future RCTs will compare cost-effectiveness with alternative techniques .. targeted biopsy guided by advanced imaging

ACG guidelines, AJG 2015
BSG guidelines, Gut 2014
ASGE guidelines, GIE 2012

Biopsy protocol and site mapping
("detection essentials")

- HRE allows recognition of subtle superficial abnormalities
- Careful cleaning of the mucosal surface
- N-acetylcysteine, simethicone ... to disperse excess mucus and bubbles
- Repeat EGD (with sedation) if previous intolerated (full biopsy protocol)
- ↑↑ PPI therapy ... in case of esophagitis or IGD

ACG guidelines, AJG 2015
BSG guidelines, Gut 2014
ASGE guidelines, GIE 2012

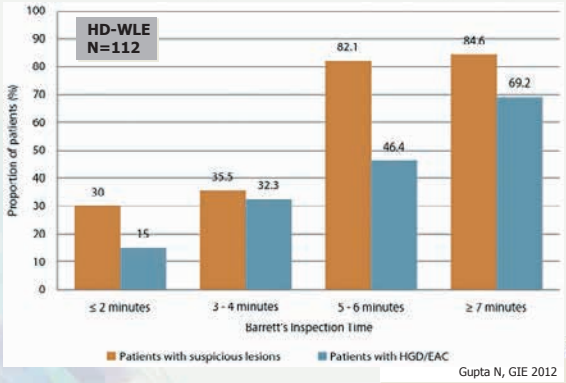
Biopsy protocol and site mapping
(„detection essentials")

- Inspect carefully by varying insufflation and desufflation
- **Retroflex the endoscope** to inspect the distal BE segment
- Targeted biopsy before random biopsies **„see more, biopsy less"**
- Distal areas should be biopsied first... to minimize obscured view from bleeding
- **Diagnostic EMR of suspected lesions better** than targeted biopsies for staging

* In suspected BE:
- at least 8 random biopsies .. to maximize the yield of IM on histology
- in short (1–2 cm) segments .. at least 4 biopsies per cm of circumferential BE, and one biopsy per cm in tongues of BE

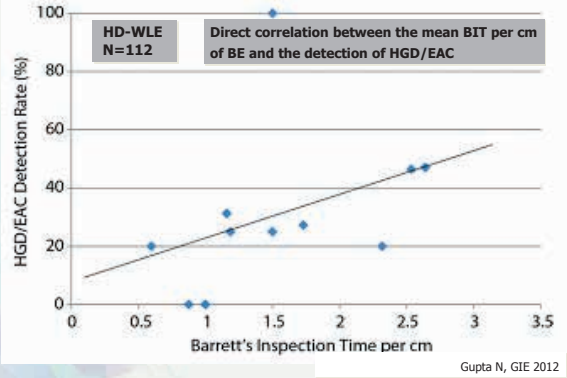
* ACG guidelines, AJG 2015
BSG guidelines, Gut 2014
ASGE guidelines, GIE 2012
Benett C, Gastroenterology 2012
Boerwinkel DF, Gastroenterology 2014

Barrett's inspection time (BIT)



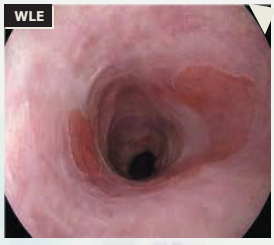
Gupta N, GIE 2012

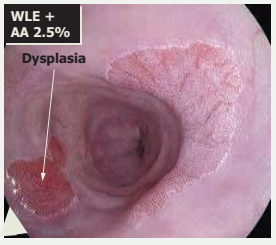
Barrett's inspection time (BIT)



Gupta N, GIE 2012

Acetic acid chromoendoscopy (AAC)





Acetowhitening + enhancement of the architecture
... disappears much sooner on the neoplastic areas

- No RCT to demonstrate benefit over WLE, but many positive observ. studies
- More data are needed

Tholoor S, GIE 2014
Longcroft-Wheaton G, Endoscopy 2013
Pohl J, Am J Gastroenterol 2010

Acetic acid chromoendoscopy (AAC)

SYSTEMATIC REVIEW AND META-ANALYSIS

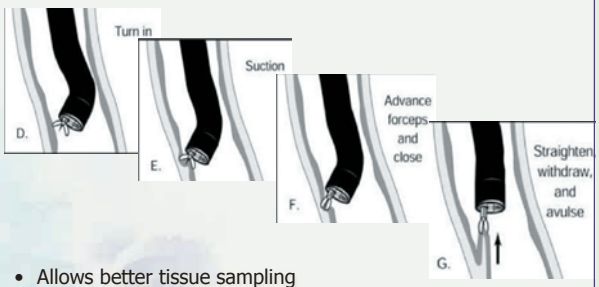
Acetic acid chromoendoscopy for the diagnosis of early neoplasia and specialized intestinal metaplasia in Barrett's esophagus: a meta-analysis

Marina Coletta, MD,[1,2] Samed S. Sami, MBChB, MRCP,[2,3] Arun Nachiappan, BSc (Hons),[2] Mirella Fraquelli, MD, PhD,[1] Giovanni Casazza, MD, PhD,[4] Krish Ragunath, MD, FRCP, FASGE[2]
Milan, Italy; Nottingham, United Kingdom

Gastrointest Endosc 2016; 83: 57-67

- AAC has an overall high dg. accuracy for detecting HGD/EC in BE
  - 9 studies, n = 1,379; pooled sensitivity 0.92, specificity 0.96
- For SIM characterization, AAC sensitivity is very high but has poor specificity ... histological confirmation is necessary
  - 8 studies, n= 516, pooled sensitivity 0.96, specificity 0.69

The „turn-and-suck“ biopsy technique



- Allows better tissue sampling
  - larger, more adequate samples with better orientation

Levine DS, Reid BJ. GIE 1991

Biopsy forceps

- The larger, the better

- Specimen size, quality, orientation

Jaw O.D. (mm)	2.2	2.4	2.8
Min Work Channel	2.8	2.8	3.2
		Standard endoscope	Therapeutic

- **Orig. Seattle protocol** based on the use of a therap. endoscope + jumbo forceps — Levine DS, AJG 2000
- Jumbo forceps superior to standard or large capacity — Martinek J, UEGW 2013; Buscaglia JM, GIE 2012; Komanduri S, GIE 2009
  - BUT problematic maneuverability and tissue sampling with therapeutic scope
    - * Jumbo theoretically can be used with a standard endoscope — Gonzales S, GIE 2010

Biopsy forceps

- The larger, the better

..BUT

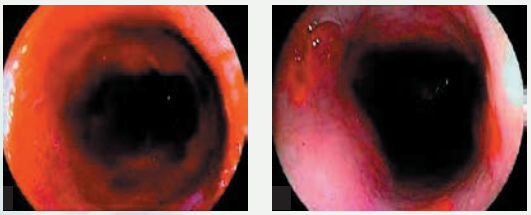
Jaw O.D. (mm)	2.2	2.4	2.8
Min Work Channel	2.8	2.8	3.2
		Standard endoscope	Therapeutic

➢ **ASGE recommend to use the Large Capacity forceps**
- Advantage of an increased tissue sample size
- Still compatible with standard 2.8 mm EGD scopes
- Better maneuverability and patient tolerance

ASGE guidelines, GIE 2012

Spraying of diluted adrenalin before biopsy

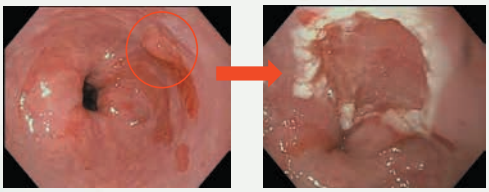
- RCT, N=40 adrenalin (1:20 000)



- "Dry biopsy" technique is safe, and facilitates thorough performance of systematic 4QB mapping of BE by improvement of visibility + reduce the time of sampling

Pohl J, Endoscopy 2008

EMR is an essential staging procedure



- Mucosal abnormalities (nodule) should be sampled separately.. **preferably with EMR**
  - In case of inability ... refer to a tertiary care center

ACG guidelines, AJG 2015

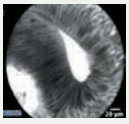
- Prosp. study of 75 pts with biopsy-proven HGD/EAC
  - EMR **altered the original grading or staging** in 48% of pts (down 28%, up 20%)

Moss A, Am J Gastroenterol 2010

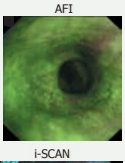
Advance endoscopic imaging

- Can we replace "random biopsies" ?
  - Decreasing biopsy number
  - Increasing diagnostic yield

CLE

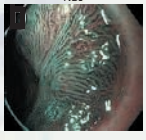


AFI

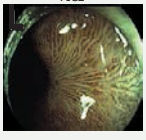


Indigo carmine

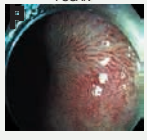
NBI



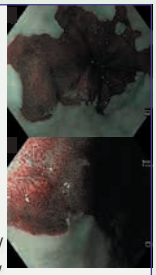
FICE



i-SCAN



Advance endoscopic imaging



NBI – Narrow Band Imaging

- The most extensively studied "virtual CE" technique
- HD-WLE standard Seattle protocol vs. NBI targeted
  - N = 123, 3 tertiary referral international centers
  - NBI: fewer biopsies per patients /3.6 vs. 7.6 ($p < 0.001$)/
  - NBI detected more dysplasia /30% vs. 21 % ($p < 0.01$)/
  - Normal NBI pattern was truly normal

Sharma P, Gut 2013

- Only moderate interobserver agreement for the interpretation
- Require high level of endoscopic expertise

Advance endoscopic imaging

- **Chromoendoscopy** (Methylene blue, Indigo carmine)
  - Not better, based on meta-analyses

Ngamruengphong S, GIE 2009

- **Virtual chromoendoscopy** (i-SCAN, FICE)
  - Insufficient data
- **Autoflorescent Imaging**
  - High sensitivity BUT high false positive rate (80%)

Kara MA, GIE 2005

- **CLE, Spectroscopy, OCT, molecular imaging**
  - Further studies are needed

Advance endoscopic imaging

… "**are not superior to standard WLE** in BE surveillance and are therefore not recommended for routine use"

(Recommendation grade A)

BSG guidelines, Gut 2014
ACG guidelines, AJG 2015

Conclusions

- Tissue sampling is the cornerstone for dg and management of pts with BE
- Essentials for appropriate "routine" clinical practice
  - Standard endoscope, HD-WLE, large capacity forceps
  - Adherence to Seattle protocol
  - See more, biopsy less, do it slowly, do it right
  - Helpful additions: Acetic acid, adrenalin
  - "Turn-and-suck" technique
  - Diagnostic EMR of suspected lesions better than targeted biopsies for staging
  - Learn to use virtual CE (NBI, FICE, i-SCAN)
- Advanced endoscopic imaging
  - more data needed, reproduction and validation of the findings

IS POEM A VALID METHOD FOR THE TREATMENT OF ACHALASIA PATIENTS?

Hubert PIESSEVAUX

Cliniques universitaires St-Luc, Université catholique de Louvain, Brussels; Belgium

In 2007 Pasricha published a landmark innovative paper reporting his experience of successful endoscopic cardiomyotomy in pigs. Subsequently Inoue *et al*. applied the technique for the first time in humans in 2009. The POEM technique was born and had an unprecedented fast development in the history of gastrointestinal endoscopy. It is also interesting to note that the development and implementation of this technique followed a more rigorous approach compared to other surgical and endoscopic techniques.

The initial enthusiasm spread from Japan to the western world and several case series were published from 2012 onwards focusing initially on **feasibility** and immediate **efficacy** (Stavropoulos 2010, von Renteln 2012, Costamagna 2012, …).

Retrospective comparative studies with Laparoscopic Heller Myotomy (LHM) showed similar **early results** as evaluated by the drop in Eckardt Score and several other per- and post-operative measures of **efficacy** (drop in IRP4s or Barium Esophagogram) or of **morbidity** (length of stay, pain scores, complication rates, …).

Subsequently indications of the procedure were expanded to patients with failure of LHM or pneumatic dilatation (PD), type III achalasia or even esophageal spastic disorders such as jackhammer esophagus and diffuse esophageal spasm.

Several technical variants were suggested, but most authors still follow the initial technique described by Inoue.

Recently the attention has been focused on **post-POEM reflux disease**. Objective signs of gastro-esophageal reflux can be found in as many as 60% of patients (Shiwaku 2015) but usually symptoms can be handled relatively easily with PPI therapy. There is still an ongoing debate whether an anterior or posterior tunnelling approach differ in this regard.

A second point of attention is the **training** for this procedure. There is evidence that endoscopists with ESD skills progress faster. The number of procedures to master the technique ranges from 40 to 60 (Patel 2015).

While several **reviews and meta-analyses** seem to indicate favorable short and medium term outcomes compared to traditional approaches (LHM and PD) (Talukdar 2015), equivalence or superiority of POEM will only be established once the results of the ongoing prospective **randomized trials** (NCT01601678, NCT02025790, NCT01768091, NCT01793922, NCT02138643, NCT02606578, NCT02518542, NCT02663206) that compare POEM to LHM, PD, Botox injection or stenting will be available.

The originality and efficacy of the POEM approach for achalasia has generated innovative ideas to treat other conditions such as **gastroparesis** (endoscopic pyloromyotomy – Chaves 2014) or **submucosal tumors** (Xu 2012).

Piessevaux H. Is POEM a valid method for the treatment of achalasia patients? In: *11th International Symposium of Gastroenterology, Saint Petersburg, Russia, 12–14 May 2016*. [online].
Available from URL: http://www.promedcs.eu/sites/default/files/abstractbook_2016.pdf

11th International Symposium of GASTROENTEROLOGY
12–14 May 2016, Saint Petersburg, Russia

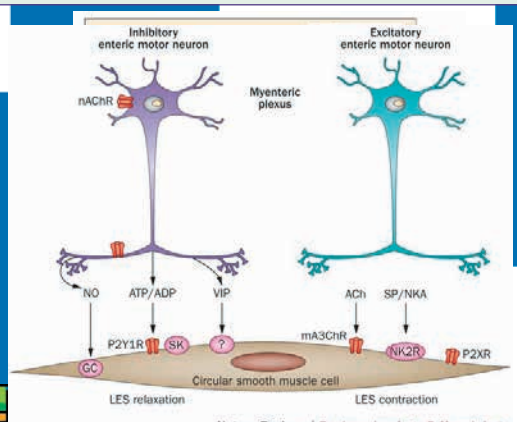
IS POEM A VALID METHOD FOR THE TREATMENT OF ACHALASIA PATIENTS?

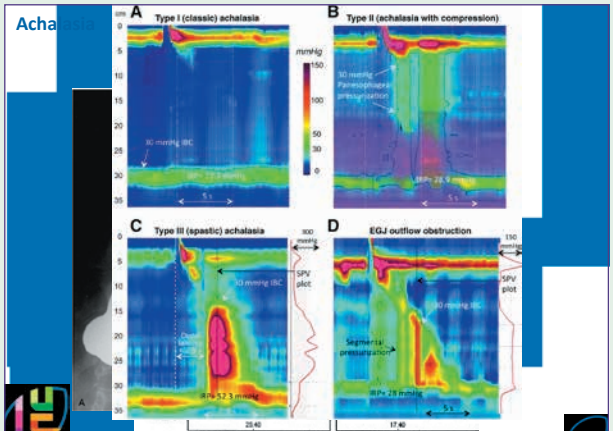
Hubert Piessevaux MD PhD

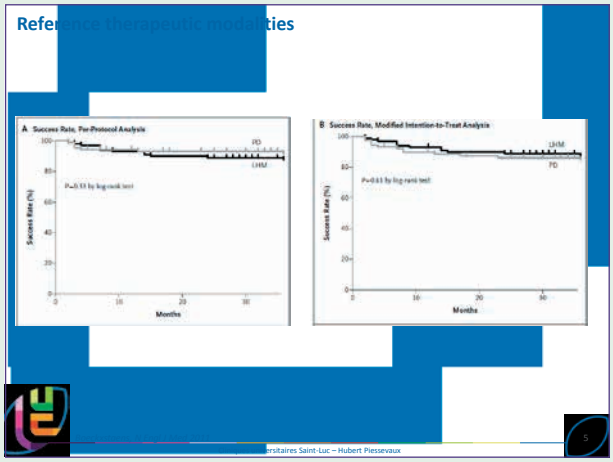
Cliniques universitaires St-Luc, Brussels
BELGIUM

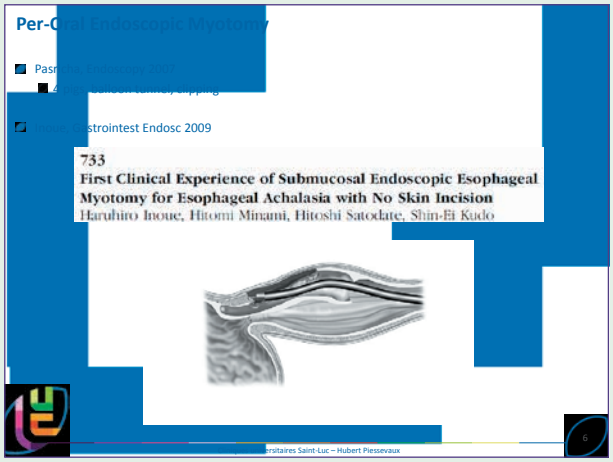
OUTLINE

- Pathophysiology of achalasia
- Reference treatment modalities
- History of POEM
- Indications – special situations
- Results
- Complications

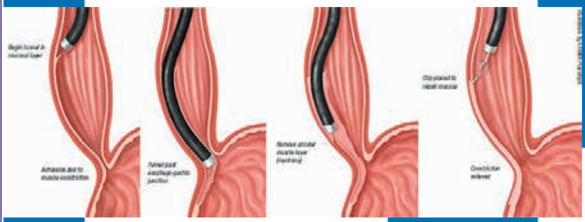








Per-Oral Endoscopic Myotomy



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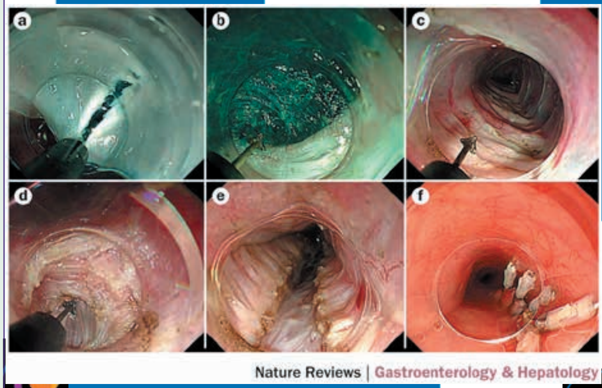
Per-Oral Endoscopic Myotomy



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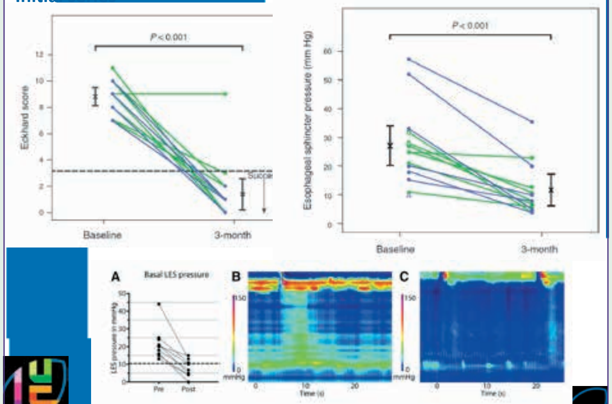
Initial series



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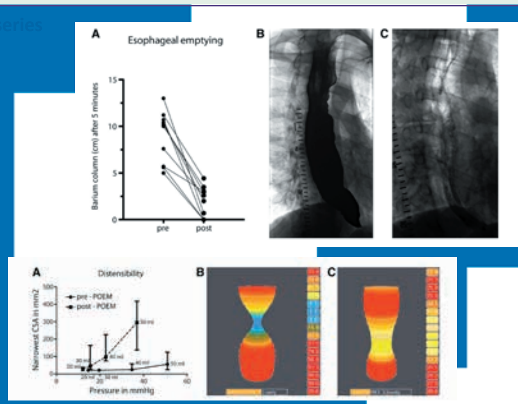
Initial series



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10

Comparative studies (non-randomized)

Perioperative outcomes

	POEM	LHM	p value
Median (range) operative time (min)	113 (88–220)	125 (90–195)	**<.05**
Myotomy length (cm)	9 (6–14)	8.5 (7–10)	.18
EBL (ml)	≤10 in all cases	50 (10–250)	**<.001**
Clips required to close mucosotomy	9 (7–17)	–	
Veress needle decompression of pneumoperitoneum	7 (39 %)	–	
Major complications (grade IIIb)	1 (6 %) - Esophageal perforation	1 (2 %) - Esophageal perforation	.45
Minor complications (grade I)	3 (17 %) - Subcutaneous emphysema - Atrial fibrillation - Urinary retention	7 (13 %) - Anterior vagus nerve division - Splenic capsule tear - Aspiration - Atrial fibrillation - Urinary retention ×2 - Readmission for chest pain	.71
Length of stay (days)	1 (1–13)	1 (1–19)	.63

ed value represents significance

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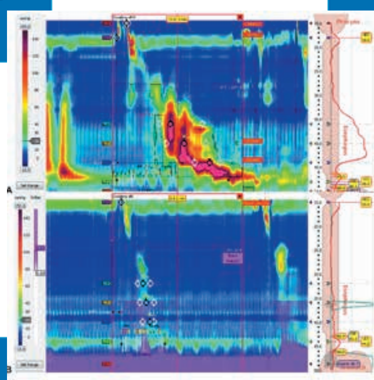
11

Expansion of indications

- Prev
  - sophagitis
  - challenging
- sorders
  - khammer
  - astic achalasia'



2014

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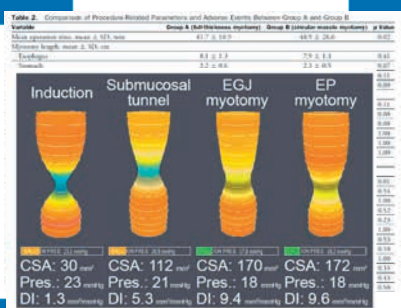
Technical variants

- Circ thic
  - pective analysis
- myotomy



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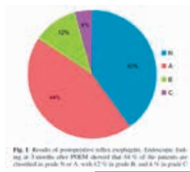
What about post-POEM Reflux?

- Prev
- e of symptoms
  variable (bias?): 0-60%
- nterior or posterior



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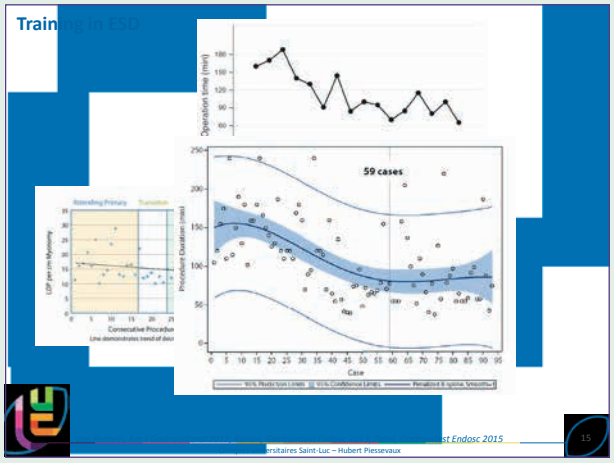

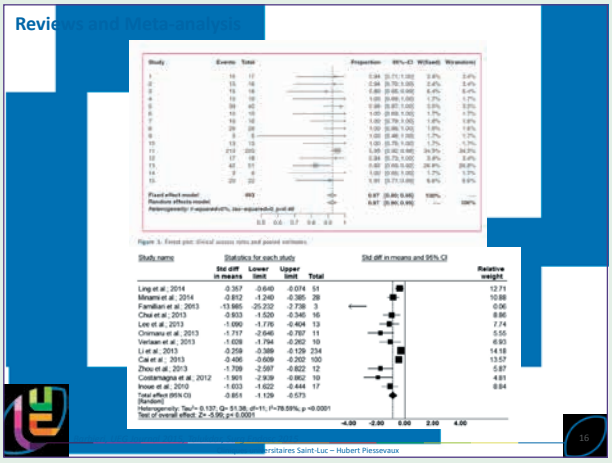

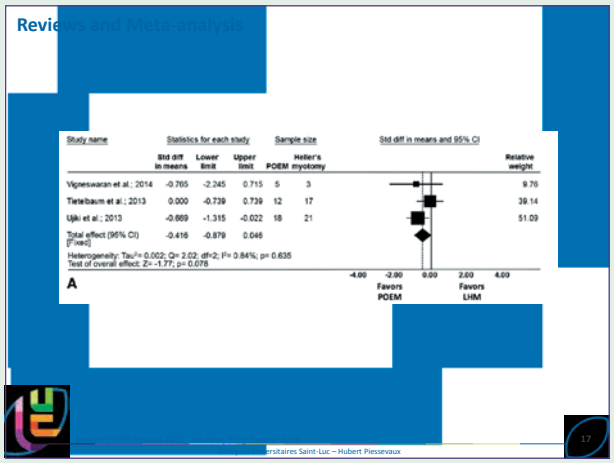

SUMMARY

- POEM is effective
  - In controlling symptoms
  - In improving objective parameters of the disease
- POEM appears safe
- POEM needs training but in reasonnable numbers
- We eagerly wait the results of randomized trials to advice patients in choosing the best therapy (vs. LHM and PD)
- POEM has opened new perspectives in therapeutic endoscopy and represents the first example of NOTES

PROGRESS IN CONSERVATIVE THERAPY IN IBD

Milan LUKAS

ISCARE I.V.F. a. s., Clinical Center Lighthouse, Prague; Czech Republic

The biological therapy due to anti-TNFα agents (infliximab, adalimumab) revolutionized the management and monitoring IBD patients at the beginning of millennium. Despite the growing knowledge regarding the optimal use these monoclonal antibodies, their application in the everyday clinical practice is still far from the optimal. There is a reason that numerous a new compounds are under the evaluation in clinical trials. We recognized some major limitations in anti-TNFα therapy in patients with ulcerative colitis and Crohn's disease. Primary and secondary non-response represents the crucial clinical problems in the real life. More than 20% of IBD patients don't response to introduction of anti-TNFα therapy and more than 50% initially responding patients lose the clinical effects with duration of treatment period. The systemic immunosuppressive effects on these monoclonal antibodies is associated with relatively frequent side effects especially an opportunistic infections. The cost of the biologics and significant economic burden are reasons for the certain restriction in access to anti-TNFα therapies in the economical poorer countries. Introduction of biosimilar infliximab recently had a positive impact in these regards induced a cost reduction and increased possibility of biological therapy for more IBD patients. A new drug class (anti-integrins) became available with the approval of vedolizumab, which is monoclonal antibody against α4β7 integrins. The optimal positioning in therapeutic armamentarium and long-term efficacy of these drugs remain to be elucidated. Another compound – etrolizumab is a human monoclonal antibody which blocks both α4β7 and anti-Eβ7 integrins. It was shown to be efficacious in induction of remission in moderately to severe ulcerative colitis. Ustekinumab is a monoclonal antibody blocking of interleukin-12 and interleukin-23 through their common p40 subunit. It has been shown that these drugs is very effective in those Crohn's disease patients those failed to anti-TNFα therapy. A clinical trials phase 3 are going on in both ulcerative colitis and Crohn's disease patients. Tofacitinib is an oral Janus kinase inhibitor having also an interleukin-6 blocking activity. Positive results have been published in patients with ulcerative colitis but not in patients with Crohn's disease. Recently, some innovation in conventional therapy has been introduced into the clinical practice. To improve the release the active drugs (budesonide or mesalazine) it can be coupled with a colonic release system MMX (Multi-Matrix-System) that provides targeted drug delivery to the entire colon. These a new technology is utilized in mild to moderate ulcerative colitis patients those failed to high dose mesalazine therapy. We have already learned that early patient stratification, optimized long-term therapy, tailored therapeutic strategy and regular and objective disease monitoring are important presumptions how to achieve the best therapeutic outcomes.

Lukas M. Progress in conservative therapy in IBD. In: *11th International Symposium of Gastroenterology, Saint Petersburg, Russia, 12–14 May 2016*. [online].
Available from URL: http://www.promedcs.eu/sites/default/files/abstractbook_2016.pdf

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12–14 May 2016, Saint Petersburg, Russia

PROGRESS IN CONSERVATIVE THERAPY IN IBD

Milan Lukáš

IBD Clinical and Research Centre, ISCARE
1st Medical Faculty Charles University
Prague

CZECH REPUBLIC

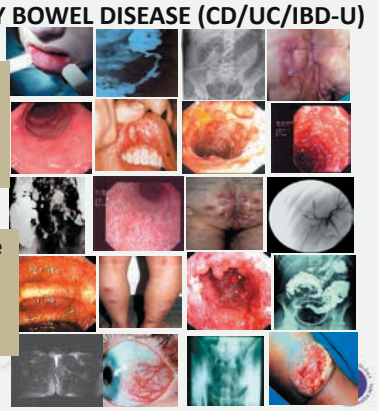
LECTURE OBJECTIVES

- IBD introduction
- Budesonide story
- Biosimilar infliximab
- New biologic drugs
- Patients monitoring and stratification

INFLAMMATORY BOWEL DISEASE (CD/UC/IBD-U)

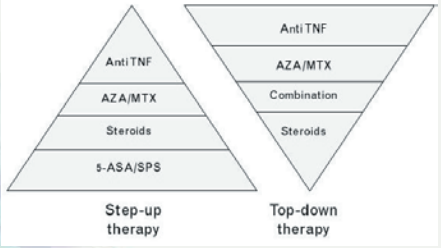
Complex disease
- small/large bowel
- perianal region
- extraintestinal organs
- metabolic and septic issues

Currently uncurable
- frequently used surgery
- suboptimal drugs efficacy
- common side effects



CURRENT MEDICAMENTS THERAPY IN IBD

Conventional	Biological therapy
• low-cost	high cost
• easily available	access restricted
• less effectivity	higher effectivity



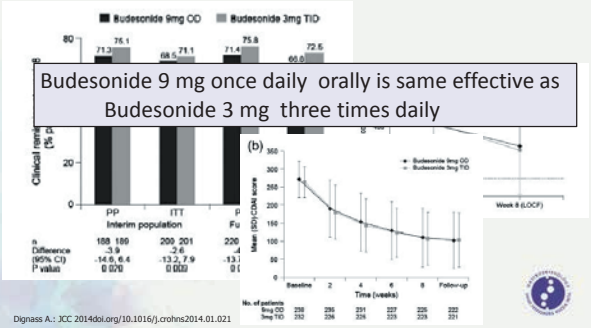
Budesonide story

BUDESONIDE THERAPY INNOVATION

Budesonide	9 mg	Sachet	Crohn´s disease (L1/L3)
Budesonide	9 mg	MMX	Ulcerative colitis (E2-E3)
Budesonide	2 mg	Rectal foam	Ulcerative colitis (E1)

6

Mild to moderate CD therapy innovation

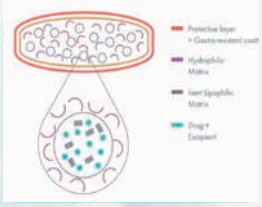


Budesonide 9 mg once daily orally is same effective as Budesonide 3 mg three times daily

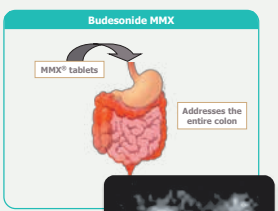
Dignass A.: JCC 2014doi.org/10.1016/j.crohns2014.01.021

Therapeutic innovation in UC: mild to moderate BUDESONIDE^{MMX}

MMX concept



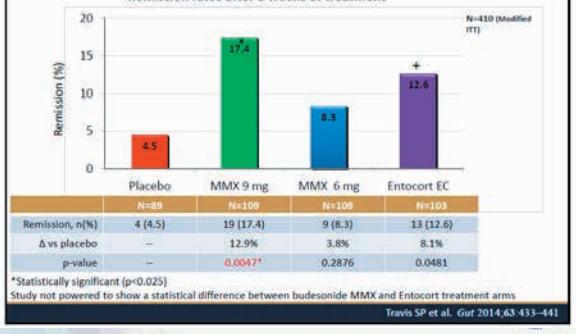
Site of action



MMX: multi matrix; UC: ulcerative colitis.

Colonic Dispersal of ^{153}Sm Labelled Budesonide MMX

Budesonide MMX® phase 3 study results (EU) primary efficacy endpoint

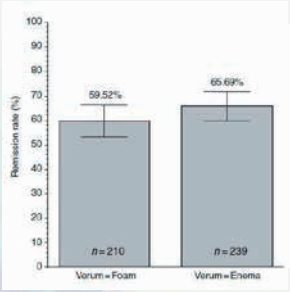


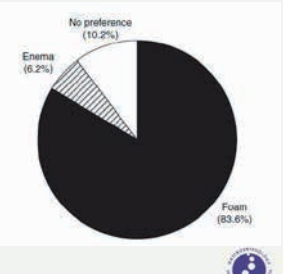
	N=89	N=109	N=109	N=103
Remission, n(%)	4 (4.5)	19 (17.4)	9 (8.3)	13 (12.6)
Δ vs placebo	--	12.9%	3.8%	8.1%
p-value	--	0.0047*	0.2876	0.0481

*Statistically significant (p<0.025)
Study not powered to show a statistical difference between budesonide MMX and Entocort treatment arms

Travis SP et al. *Gut* 2014;63:433–441

Local treatment innovation in UC





V. Gross: APT 2006; 23: 303-312

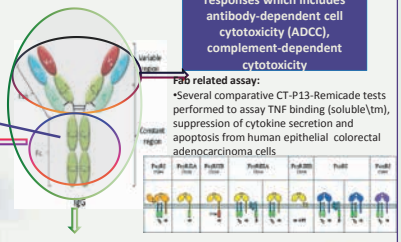
BIOSIMILAR INFLIXIMAB

NAIVE IBD PATIENTS
SWITCHED IBD PATIENTS

CT-P13 MECHANISMS OF ACTION KNOWN TODAY : APPROVED INDICATIONS (RA, AS, IBD)

Primary mechanism TNFα neutralisation binding to TNFα and inhibition of cell signaling for proliferation.

Secondary mechanism: activation of the immune responses which includes antibody-dependent cell cytotoxicity (ADCC), complement-dependent cytotoxicity



An increase in fucosylated mAbs was observed in CT-P 13 compared to Remicade

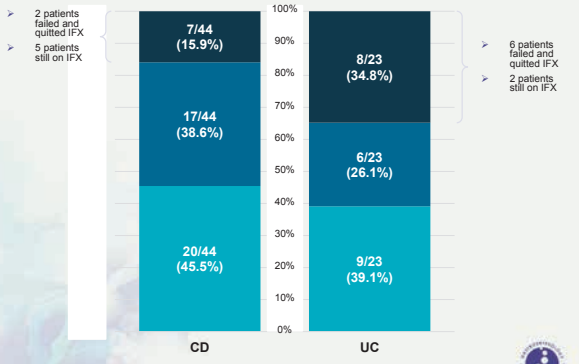
Fab related assay:
•Several comparative CT-P13-Remicade tests performed to assay TNF binding (soluble\tm), suppression of cytokine secretion and apoptosis from human epithelial colorectal adenocarcinoma cells

Fc receptor related assay:
•Several comparative CT-P13 Remicade tests performed in order to evaluate binding to Fcγ receptors *In vitro* and *ex vivo* even using CD patient serum

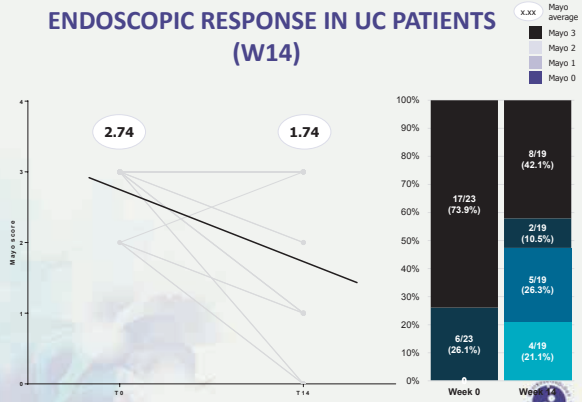
Fc-F(ab')2 related:
•ADCC and CDC comparative CT-P13-Remicade tests performed to evaluate ADCC and CDC cytotoxicity using healthy donor and CD patients serum (effector cell NK and whole blood)

EMEA, CT-P13 European Public Assessment Report, EMA/CHMP/394891/2013, 27 June 2013

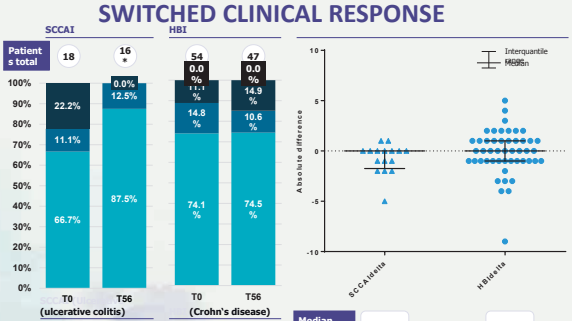
RESPONSE EVALUATION



ENDOSCOPIC RESPONSE IN UC PATIENTS (W14)



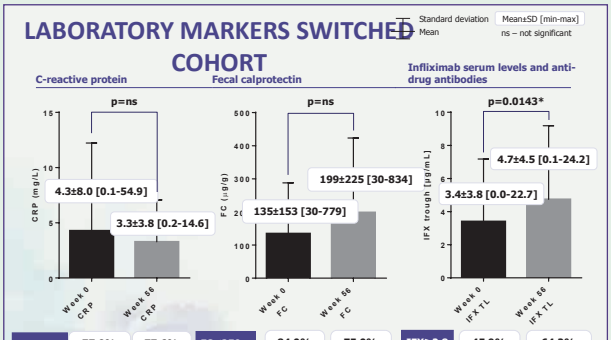
SWITCHED CLINICAL RESPONSE



Median (range)	0 (-5, 1)	0 (-9, 5)

Median difference of HBI/SCCAI between week 0 and week 56

LABORATORY MARKERS SWITCHED COHORT



CRP≤5mg/L	77.0% (57/74)	77.6% (52/67)	FC≤250µg/g	84.0% (42/50)	75.0% (36/48)	IFX≥2.8µg/mL	45.9% (34/74)	64.2% (43/67)
						ADA positive	9.5% (7/74)	

BIOSIMILAR INFLIXIMAB – LOCAL EXPERIENCE

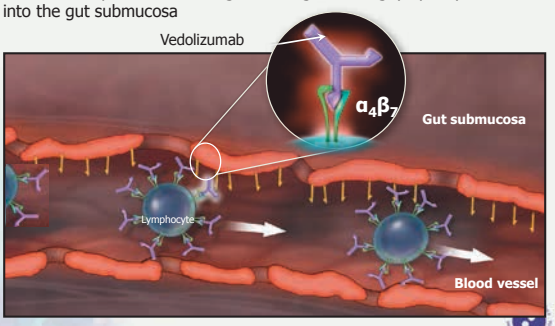
- CT-P13 therapy in naive IBD patients has a positive clinical response in 84% (CD) resp. 66% (UC) patients
- Switch from original infliximab to CT-P13 after 56 weeks is not associated with any negative signal in terms of efficacy and side effects
- Immunogenicity of CT-P13 therapy seems to be on the same level as an original infliximab

New biologic drugs for IBD

Focus on vedolizumab

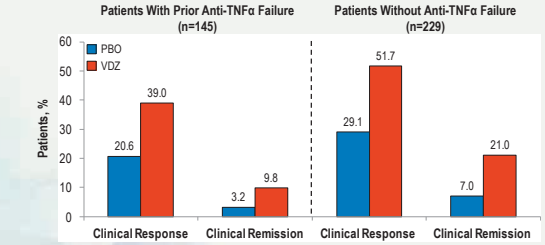
SELECTIVE RECEPTOR BLOCKADE

Vedolizumab prevents transmigration of gut-homing lymphocytes into the gut submucosa



Soler D., *et al.* J Pharmacol Exp Ther 2009; 330(3): 864–875.

GEMINI I: BIOLOGIC NAIVE VS ANTI TNF FAILURES



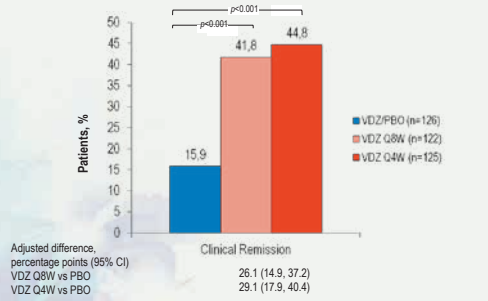
Mean Δ% (95% CI) VDZ vs PBO	18.4 (3.9, 32.9)	6.6 (–9.8, 22.8)	22.7 (10.1, 35.3)	14.0 (5.4, 22.6)

PBO, placebo; TNF, tumor necrosis factor; VDZ, vedolizumab.

Rutgeerts P et al. Presentation at the UEGW 20th Annual Meeting 2012.
Feagan B et al. 8th Congress ECCO 2013; 7: P513. 20

GEMINI 1: MAINTENANCE THERAPY AT WEEK 52

Primary Outcome: Maintenance ITT Population



Adjusted difference, percentage points (95% CI)	
VDZ Q8W vs PBO	26.1 (14.9, 37.2)
VDZ Q4W vs PBO	29.1 (17.9, 40.4)

Derived from: Feagan BG et al. N Engl J Med 2013; 369: 699-710.

CS, corticosteroid; PBO, placebo; VDZ, vedolizumab.

EVIDENCE – BASED CHOICE OF ANTI-TNFA AND ANTI-INTEGRIN AGENT IN IBD

	Anti-TNF	Anti-integrin
UC		
Induction/maintenance UC	■/■	■/■
Steroid refractory fulminant UC	■	
Steroid refractory UC (post-hoc)	■	■
Early UC/late UC (post-hoc)	■	■
Safety in UC	■	■
CD		
Induction/maintenance luminal CD	■/■	■/■
Perianal fistulizing CD	Infliximab	■
Early luminal/late luminal CD (post-hoc)	■/■	■/■

Danese S, Panes J: Gastroenterology 2014; 147:981-989

Patients stratification and monitoring

THE NEED TO LOOK FOR POOR PROGNOSTIC FACTORS

Table 2. Clinical risk factors for complicated IBD

CD	UC
Ileal disease	Extensive colitis
Upper gastrointestinal extent	Young age at diagnosis
Smoking	
Complicated behavior (stricturing or penetrating)	
Young age at diagnosis	
Perianal disease	

Zallot and Peyrin-Biroulet. Dig Dis 2012

RISK MATRIX MODEL FOR PREDICTION OF COLECTOMY: THE IBSEN COHORT

- Population based study of 464 UC patients
- Ten years FU / 45 colectomized patients, multiple regression to select risk factors, fitted into a prediction model

Correct prediction in 90.3% of the cases

		ESR: Under 30	ESR: Over 30		
Age at diagnosis	<40 years	8.0% 95% CI [5.5%–10.5%]	29.9% 95% CI [25.8%–34.1%]	Yes	Systemic steroids at diagnosis
	>40 years	2.3% 95% CI [1.0%–3.7%]	10.5% 95% CI [7.7%–13.5%]	No	
		Proctitis and left-sided colitis	Extensive colitis		

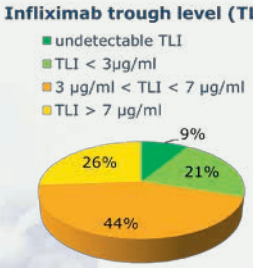
Extent of disease at diagnosis

Conclusions: Risk is 15 times higher in young patients, with extensive colitis, ESR >30 and who needed CS at diagnosis.

Cvancarova M et al. Gut 2010;59 Suppl III:A36

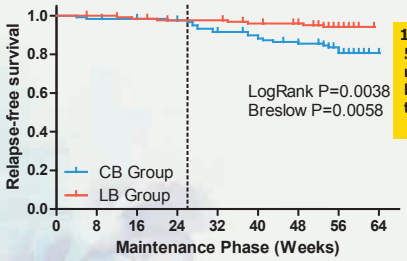
THERAPEUTIC DRUGS MONITORIG

TAXIT: 257 pts with sustained response to IFX



Vande Casteele: Gastro 2015;148:1320

SECONDARY GOAL OF TAXIT "RELAPS FREE SURVIVAL"



17.3% of CB Group *vs.* 5.5% of LB Group needed rescue therapy by the end of the maintenance phase

Vande Casteele: Gastro 2015;148:1320

SUMMARY

- **Conventional therapy changed in the last couple years: aiming at once daily dosage, minimalize side effects and improve efficacy and tolerability**
- **Introduction of biosimilar infliximab significantly reduced cost and increased avalaibility of biological therapy for higher proportion of patients**
- **New biologic drug vedolizumab was introduced on the market in the most European countries**
- **A new approach including patients stratification and therapeutic drug monitoring is utilized in clinical practice**

CAN WE USE THE AMINOSALICYLATES IN CLINICAL PRACTICE IN IBD PATIENTS?

Grazyna RYDZEWSKA

Clinical Department of Internal Medicine and Gastroenterology with Inflammatory Bowel Disease Unit, Central Clinical Hospital Ministry of Interior in Warsaw; Poland

Oral 5-aminosalicylate (5-ASA) in minimal effective dose 1.2 g per day, are still the first line treatment of mild to moderate ulcerative colitis, with high rates of efficacy in induction and maintenance of remission. Mesalazine exerts therapeutic effect through local topical activity at the inflamed mucosa. Oral mesalazine in unaltered form is almost entirely absorbed by the small intestines, with very little intact drug reaching the colon, so the main goal of the different formulations is to optimise drug delivery to the affected colon and minimise systemic absorption.

Rectal 5-ASA are used in proctitis and alternatively in left-side colitis. A combination of oral and rectal 5-ASA are still the treatment of choice for left-side colitis.

Although sulfasalazine is equally effective, other oral 5-ASA preparations are preferred for toxicity reasons.

The effect of mesalazine in Crohn's disease is not so evident, and the role of mesalazine in reducing postoperative reccurence is not clinically relevant.

Various formulations of oral 5-ASA are available, and selection of the most appropriate formulation must incorporate factors such as disease distribution, efficacy, side effect profile, pill burden, patient preference and health economics.

On the other hand, mesalazine, but not sulfasalazine, can reduce the risk of colorectal neoplasia in patients with IBD. The effective dose of mesalazine in chemoprevention in IBD patient is more than 1.2 g/day. No benefit of mesalazine in colorectal cancer prevention was note in population-based study.

Rydzewska G. Can we use the aminosalicylates in clinical practice in IBD patients? In: *11th International Symposium of Gastroenterology, Saint Petersburg, Russia, 12–14 May 2016*. [online].
Available from URL: http://www.promedcs.eu/sites/default/files/abstractbook_2016.pdf

11th International Symposium of GASTROENTEROLOGY
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CAN WE USE THE AMINOSALICYLATES IN CLINICAL PRACTICE IN IBD PATIENTS?

Grażyna Rydzewska

Gastroenterology Dept. with IBD Subdivision, Central Clinical Hospital of Ministry of Inferior and Administration, Warsaw

POLAND

SULFASALAZINE AND 5-AMINOSALICYLATES IN IBD TREATMENT

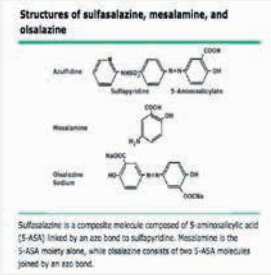
- Mechanism of action
- 5-ASA in the treatment of ulcerative colitis
- 5-ASA in the treatment of Crohn disease
  - prophylaxis of postoperative Crohn disease
- Chemoprevention with 5-ASA

SULFASALAZINE AND 5-AMINOSALICYLATES IN IBD TREATMENT

- **Mechanism of action**
- 5-ASA in the treatment of ulcerative colitis
- 5-ASA in the treatment of Crohn disease
- Chemoprevention with use of 5-ASA

SULFASALAZINE AND 5-AMINOSALICYLATES – MECHANISM OF ACTION

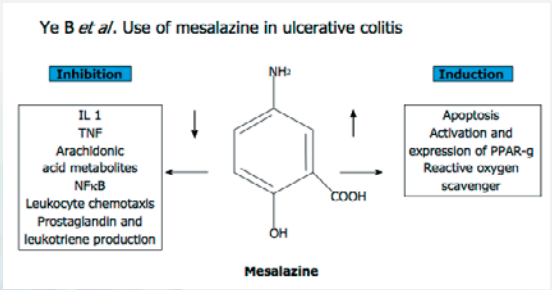
- Salicylazosulfapyridine (sulfasalazine) was originally proposed as a treatment for rheumatoid arthritis in 1950
- It was subsequently discovered that sulfasalazine was also efficacious in treating IBD, particularly ulcerative colitis
- The 5-aminosalicylic acid (5-ASA) medications were developed because many patients were intolerant of or allergic to sulfasalazine



SULFASALAZINE AND 5-AMINOSALICYLATES – MECHANISM OF ACTION

- Although the precise mechanism responsible for the clinical efficacy of 5-aminosalicylic acid (5-ASA) compounds is not known, they are thought to act topically.
- The following mechanisms have been proposed:
  - Inhibition of cytokine synthesis
  - Inhibition of prostaglandin and leukotriene synthesis
  - Free radical scavenging
  - Immunosuppressive activity
  - Impairment of white cell adhesion and function

SULFASALAZINE AND 5-AMINOSALICYLATES – MECHANISM OF ACTION



Ye B., et al. World J Gastrointest Pharmacol Ther 2015 November 6; 6(4): 137–144.

SULFASALAZINE AND 5-AMINOSALICYLATES IN IBD TREATMENT

- Mechanism of action
- **5-ASA in the treatment of ulcerative colitis**
- 5-ASA in the treatment of Crohn disease
- Chemoprevention with use of 5-ASA

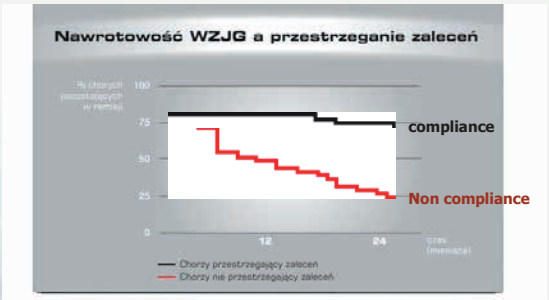
5-ASA IN THE TREATMENT OF ULCERATIVE COLITIS (PROCTITIS, PROCTOSIGMOIDITIS)

- In mild and moderate disease, topical 5-ASA are recommended in induction of remission
- For patients unwilling or unable to tolerate any topical medication, oral 5-ASA medications are recommended
- For maintenance of remission in patients who have more than one relapse a year and in all patients with proctosigmoiditis 5-ASA enema are recommended
- Patients who required oral 5-ASAs to achieve remission or who have multiple relapses on topical therapy should be continued on oral 5-ASAs to maintain remission

LEFT SIDE COLITIS, EXTENSIVE COLITIS OR PANCOLITIS

- In patients with mild or moderate disease combination therapy with oral 5-ASA medication and 5-ASA enema or foam is recommended
- In maintenance therapy oral 5-ASA and topical 5-ASA are recommended

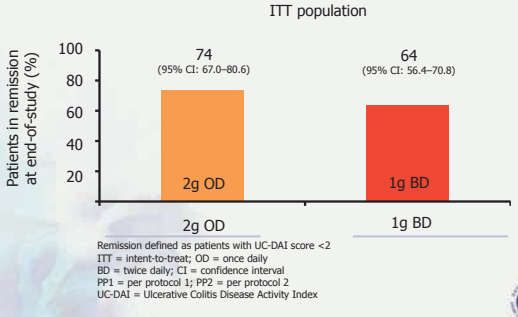
MESALAZINE IN THE MAINTENANCE TREATMENT OF UC



Kane S., et al. The American Journal of Medicine 2003; 114: 39–43.

5-ASA IN THE TREATMENT OF ULCERATIVE COLITIS

5-ASA IN THE TREATMENT OF ULCERATIVE COLITIS – PODIUM STUDY REMISSION IN THE END OF TREATMENT



Dignass A., et al. Clin Gastroenterol Hepatol 2009; 7: 762–9.

5-ASA IN THE TREATMENT OF ULCERATIVE COLITIS

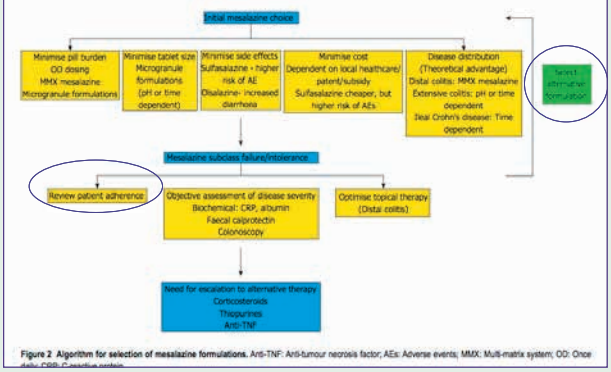
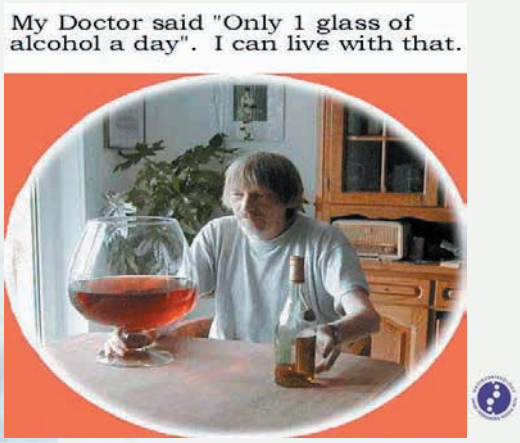


Figure 2 Algorithm for selection of mesalazine formulations. Anti-TNF: Anti-tumour necrosis factor; AEs: Adverse events; MMX: Multi-matrix system; OD: Once



5-ASA IN THE TREATMENT OF ULCERATIVE COLITIS

- oral mesalazine remains the cornerstone of management of mild to moderate ulcerative colitis
- Failure of one formulation, should not negate future use of the entire drug class
- Choosing different formulation we have to take into account economic reason, disease extension and compliance

SULFASALAZINE AND 5-AMINOSALICYLATES IN IBD TREATMENT

- Mechanism of action
- 5-ASA in the treatment of ulcerative colitis
- **5-ASA in the treatment of Crohn disease**
- Chemoprevention with use of 5-ASA

SULFASALAZINE AND 5-AMINOSALICYLATES IN THE TREATMENT OF CROHN DISEASE

- The use of 5-ASA drugs for Crohn disease is controversial
- A 2011 meta-analysis included 22 randomized trials (6 trials looking at 5-ASAs for the induction of remission, 13 for maintenance of remission, and 3 for both induction and maintenance of remission)
  - 5-ASAs were superior to placebo for the induction of remission
  - Failure to achieve remission was seen in 68 percent of patients treated with 5-ASAs compared with 75 percent of patients treated with placebo
  - In order to achieve remission in one patient with active Crohn disease, 11 patients would need to be treated

Ford A.C., Kane S.V., Khan K.J., et al. Efficacy of 5-aminosalicylates in Crohn's disease: systematic review and meta-analysis. Am J Gastroenterol 2011; 106: 617.

SULFASALAZINE AND 5-AMINOSALICYLATES IN THE TREATMENT OF CROHN DISEASE

- 5-ASA plus a glucocorticoid was not superior to a glucocorticoid alone for the induction of remission
- There was no benefit with 5-ASA treatment for the maintenance of remission.
- Mesalamine and budesonide were **similarly** effective for the induction of remission in patients with mildly to moderately active Crohn disease

Ford A.C., Kane S.V., Khan K.J., et al. Efficacy of 5-aminosalicylates in Crohn's disease: systematic review and meta-analysis. Am J Gastroenterol 2011; 106: 617.

SULFASALAZINE AND 5-AMINOSALICYLATES IN THE TREATMENT OF CROHN DISEASE - GUIDELINES

- American College of Gastroenterology and the British Society of Gastroenterology both recommend budesonide for use as first-line therapy in patients with mildly to moderately active Crohn disease
- ECCO Consensus recommends that 5-ASAs not be used for Crohn disease
- According to some data 5-ASA may be an option in patients with mild to moderate colonic (left-sided) Crohn disease
- Some experts argue that 5ASA should be tried in patients with mild Crohn disease based upon their relative safety compared with glucocorticoids, immunomodulators, and biologic agents, particularly given the potential chemopreventative benefits of 5-ASAs in patients with longstanding Crohn colitis

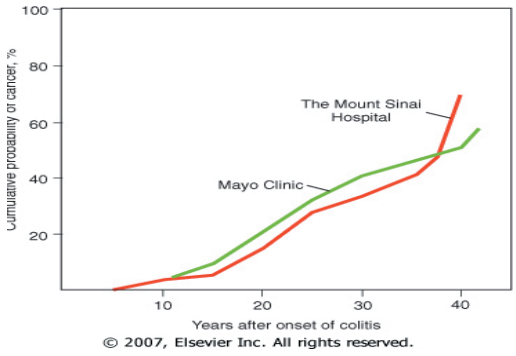
5-ASA FOR PROPHYLAXIS OF POSTOPERATIVE CROHN DISEASE

- Postoperative recurrence of CD can be defined by endoscopic findings or clinical symptoms
- Consensus has not been achieved on optimal strategies for prevention of recurrent Crohn disease after surgery
- Endoscopic findingd of recurrent Crohn disease generally precede clinical symptoms. We therefore perform an endoscopic assessment 6 to 12 months following surgery to identify recurrence in low risk patients
- Mesalamine prophylaxis is associated with a modest benefit in preventing relapse.
- This could be an option for patients who appear to benefit from mesalamine prior to resection, those without high-risk features for relapse, or those unwilling to consider agents with more side effects.

SULFASALAZINE AND 5-AMINOSALICYLATES IN IBD TREATMENT

- Mechanism of action
- 5-ASA in the treatment of ulcerative colitis
- 5-ASA in the treatment of Crohn disease
- **Chemoprevention with 5-ASA**

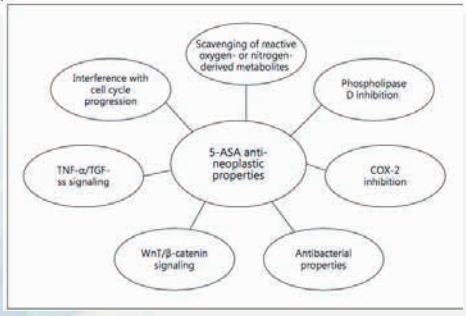
CUMULATIVE RISK OF CRC IN IBD PATIENTS



5-Aminosalicylic Acid and Chemoprevention: Does It Work?

Anthony Lopez Laurent Peyrin-Biroulet

Inserm, U954 and Department of Hepatogastroenterology, University Hospital of Nancy, Vandoeuvre-lès-Nancy, France



MESALAMINE IN CHEMOPREVENTION

- In addition to their overall antiinflammatory activity on the intestinal mucosa, 5-ASA compounds have specific effects on colorectal carcinogenesis at the molecular level
- In 2005, a landmark metaanalysis of observational studies found a protective association between 5-ASA and CRC in UC patients
- More recently, a metaanalysis failed to identify a protective effect of 5-ASA on CRC risk in non-referral populations, but in a separate analysis of 9 clinic-based studies, highlighting the chemopreventive effect of 5-ASA on CRC risk

MESALAMINE IN CHEMOPREVENTION

- In conclusion, 5-ASA therapy may reduce CRC risk by healing the mucosa of UC patients and via specific mechanisms of action at the molecular level
- Conducting a clinical trial providing the best level of evidence by comparing UC patients receiving 5-ASA treatment versus those included in a placebo arm would be unethical

Cancer in IBD

Dig Dis 2013;31:248–253
DOI: 10.1159/000353806

Anthony Lopez Laurent Peyrin-Biroulet

Inserm, U954 and Department of Hepatogastroenterology, University Hospital of Nancy, Vandoeuvre-lès-Nancy, France

CAN WE USE THE AMINOSALICYLATES IN CLINICAL PRACTICE IN IBD PATIENTS? TAKE HOME MESSAGE

- Aminosalicylates are still a cornerstone in the treatment of mild and moderate UC
- The role of 5-ASA in Crohn disease is unclear, however some experts and a lot of practising gastroenterologist are still using it
  - there is still a place for mesalamine in relapse prevention after surgery
- Mesalamine therapy may reduce CRC risk by healing the mucosa in UC patients (maybe in colonic Crohn)

LAPAROSCOPIC PROCEDURES IN IBD: LIMITS AND ADVANTAGES

Mojmir KASALICKY

Surgical Department, 2nd Medical School, Charles University and Central Military Hospital, Prague; Czech Republic and Faculty of Health Sciences and Social Work, Trnava University, Trnava; Slovakia

Aim. Surgery plays a very important role in the management of IBD. 70% to 90% of diagnosed patients with Crohn's disease (CD) eventually require surgery, usually for complications or failure of medical treatment. Approximately 40% to 50% of patients undergoing surgery are likely to need further operations within 10–15 years. Ileal pouch–anal anastomosis (IPAA), also known as restorative proctocolectomy (RPC), is the surgical near gold standard for chronic ulcerative colitis (CUC). Laparoscopic colorectal surgery (LCS) in patients with inflammatory bowel disease (IBD) is becoming a standard and feasible surgical method worldwide. Over the last decade, there have been many studies documenting the safety and feasibility of the LCS for IBD in well-selected patients.

Methods. Patients without any previous gut resection with CD often with the tight iliac stenosis and prestenotic dilatation, various colon stenoses or with ulcerative proctocolitis were indicated for the LCS. From 2009 to 2015, 154 ileocolic resections, 41 hemicolectomies, 34 subtotal colectomies and 11 restorative proctocolectomies with IPAA were performed either totally laparoscopically or laparoscopically assisted.

Results. The average time of the procedure was 105 minutes (65–295 min), average blood loss 125 ml (0–350 ml) and the conversion to laparotomy was in 8.2%. Average return time of the bowel function was 3.5 days (2–8 days) and the average hospital stay was 7.1 days (6–11days). 1 case of the early ileus due to adhesions, 5 cases incision hernia in minilaparotomy and 7 wound infections occurred.

Conclusion. In well-selected patients with IBD, thanks to superior short- and long-term outcomes, the laparoscopic approach should be considered a safe and effective method when performed by experienced surgeons especially in patient with CD. Laparoscopic IPAA is an appealing alternative to open surgery and it is performed with increasing frequency in many centers. Despite superiority of LCS for IBD in short-term perioperative outcomes and equivalence in many long-term outcomes, the steep learning curve, complex surgeries, and challenging anatomy continue to be barriers to the widespread application of LCS techniques for IBD. The advanced laparoscopic skills required and the potential difficult anatomic and operative conditions argue that these procedures should be performed at a tertiary referral center with a specialized surgeon.

Supported by MO1012.

Kasalicky M. Laparoscopic procedures in IBD: Limits and advantages. In: *11th International Symposium of Gastroenterology, Saint Petersburg, Russia, 12–14 May 2016*. [online].
Available from URL: http://www.promedcs.eu/sites/default/files/abstractbook_2016.pdf

11th International Symposium of GASTROENTEROLOGY
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LAPAROSCOPIC PROCEDURES IN IBD: THE LIMITS AND ADVANTAGE

Prof. Mojmir Kasalicky, MD, PhD.

Surgical Department 2nd Medical School Charles University and Central Military Hospital Prague

CZECH REPUBLIC

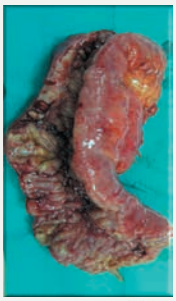
LAPAROSCOPIC SURGERY IN IBD

- MINIINVASIVE COLORECTAL SURGERY (**MIS**)

- Although many surgeons have become comfortable with MIS for benign and malignant abdominal disease, such as colon cancer and sigmoid diverticulitis, the application of laparoscopic surgery to patients with IBD, has been more slowly adopted still.

MIS IN IBD

- MIS to patients with IBD, has been more slowly adopted probably due to relative technical difficulties in IBD
  - frequent presence of chronically inflamed mesentery
  - phlegmonous inflammatory masses
  - friable tissues
  - abscesses
  - strictures
  - enteric fistulas
  - chronically dilated loops of bowel



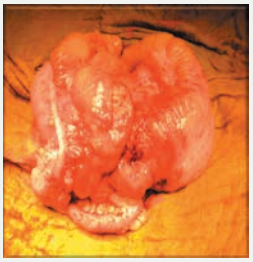
SURGERY IN IBD

- **Elective operations**
  - Advantage → to have time → Possibility of indication for the elective laparoscopic colorectal surgery in IBD (MIS)
- **Emergent** - ileus
- **Urgent -** Perforation, peritonitis, bleeding, toxic megacolon, sepsis, …

Unsuitable for MIS

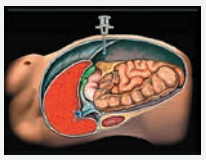
Fichera A: Laparoscopy or conventional open surgery with ileocolic Crohn's disease? Prospective study. Surgery, 2007; 142(4): 566-71.

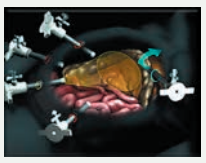
LIMITS OF MIS IN IBD



- Learning curve is longer
- Longer procedure`s time
- Impossibility of the bowel tissue palpation
- Necessity of the proper selection of the patients with IBD → MIS
- Complicated IBD disease and multiple previous abdominal operations are usually contraindicated to the MIS

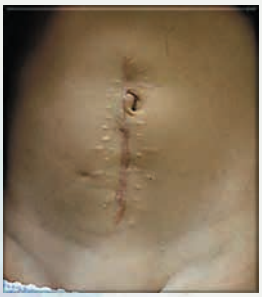
BENEFITS OF MIS IN IBD

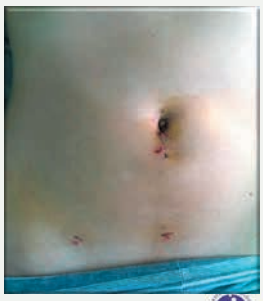




- Minimal injury of the abdominal wall, organs and tissues
- Preserving pelvic organs, …
- Minimal blood loss
- Faster restitution of the bowel function/movement
- Faster rehabilitation
- ↓ hospital stay
- ↓ adhesions
- ↓ wound complications
- Better cosmetics effect

IBD / ILEOCOLIC RESECTION OPEN SURGERY X LAPAROSCOPIC



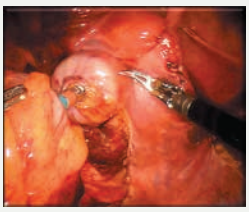


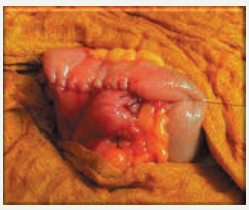
CROHN`S DISEASE LAPAROSCOPIC MIS

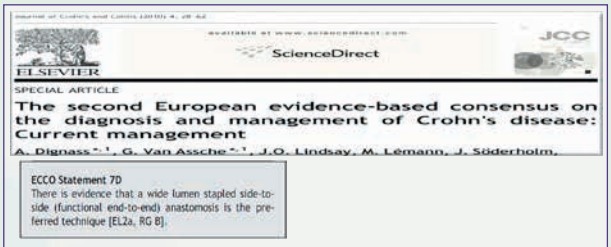
- Bowel resection
  - Ileocolic resection
  - Hemicolectomy
  - Subtotal colectomy
  - Proctectomy
  - Proctocolectomy
- Ileo/colo stomy
- Stricturoplasty
- Abscess drainage
- Fistulectomy
- Perianal CD

TECHNIQUE OF THE ANASTOMOSIS

- Completely laparoscopically
  - By staplers
  - Hand sewn
- Laparoscopically assisted
  - Anastomosis via minilaparotomy
    - Hand sewn
    - By staplers
  - Minilaparotomy
    - 4 ↔ 6 ↔ 8 cm



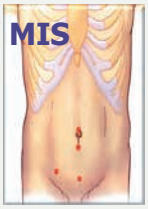


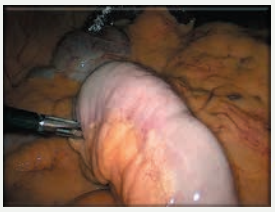


- A recent prospective cohort study showed no difference in safety and recurrence rate between hand-sewn side-to-side and stapled side-to-side anastomosis
- Wide anastomotic luminal diameter is much more important factor than the suturing technique used.

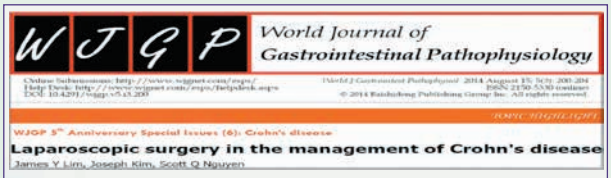
ILEO-COLIC RESECTION BY MIS

- 70 % to 90 % of patients with CD will require surgery during 10-15 years from diagnosis with the most commonly affected site as the ileocecal region.
- Laparoscopic approaches have therefore increased in prevalence in the population of patients with IBD

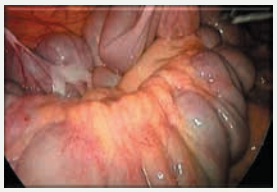


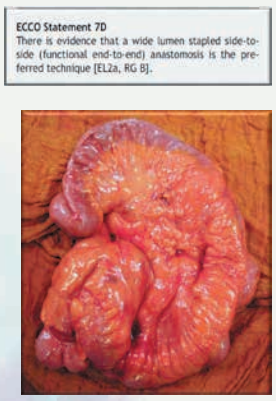


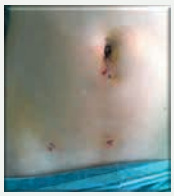
Lesperance K: National Trends and Outcomes for the Surgical Therapy of Ileocolic Crohn`s Disease: A Population-based Analysis for Laparoscopic v.s. Open Aproaches. J Gastrointest Surg, 2009,13:1251-1259.

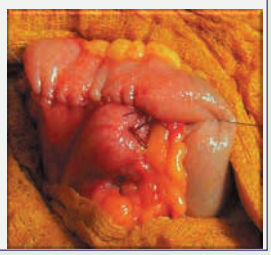


- Laparoscopic **ileo-colic** resection is nearly the new gold standard in the surgical treatment of complicated CD of terminal ileum.

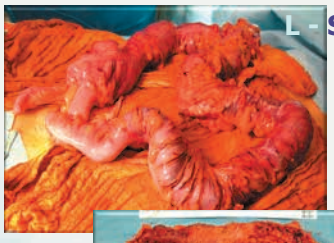


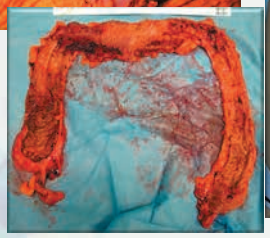


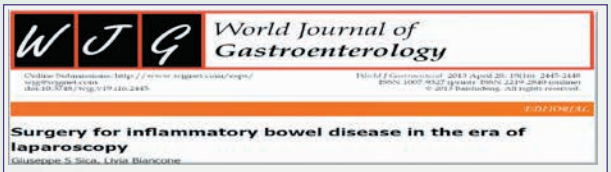




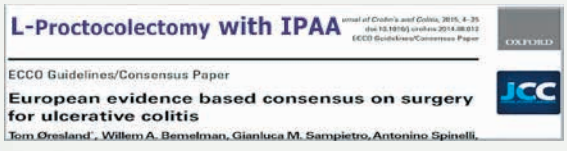
L - Subtotal colectomy



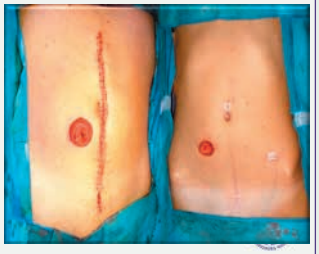




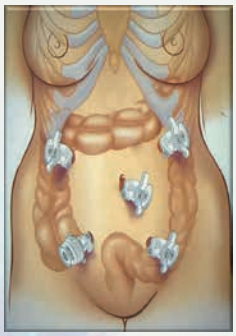
- Laparoscopic **proctocolectomy** and restorative **IPAA is** rapidly becoming the standard of care in the treatment of **UC** requiring surgery
- Number of the PC with IPAA by laparoscopy is growing at present.

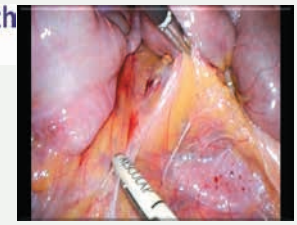


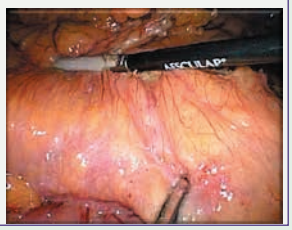
- Circular stapling IPAA 1-2 cm from the anus is recommended
- Minimal intraabdominal and pelvic adhesions
- Abdominal wall saving method
- Real very good cosmetic effect



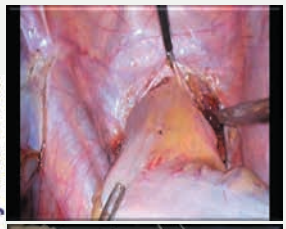
L-Proctocolectomy with IPAA

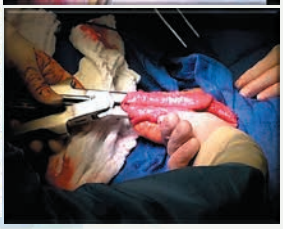


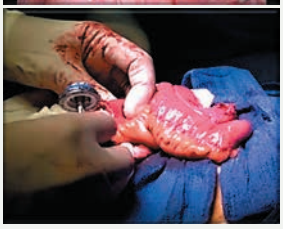




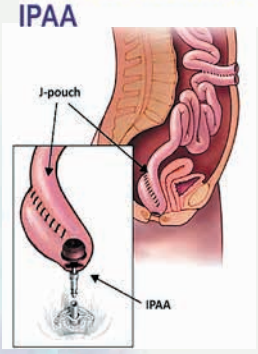
L-Proctocolectomy with IPAA

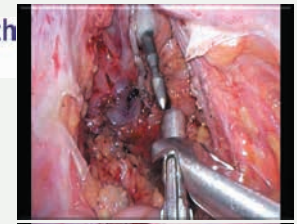


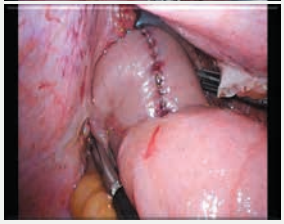




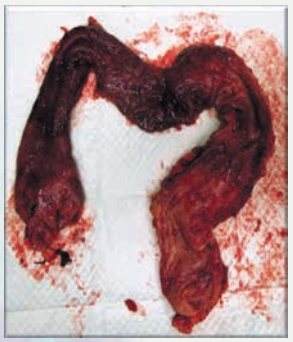
L-Proctocolectomy with IPAA

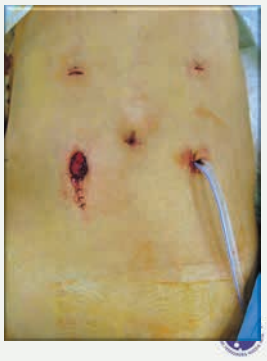






L-Proctocolectomy with IPAA

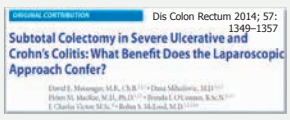




IBD – 2009-2015 - L/LA PROCEDURES

N = 238	years	range
Female - 153	38,8	17 - 62
Male - 85	34,1	18 - 61
Ø – age	31,8	17 - 65
Ø – duration IBD	7,9	1 - 25

L/LA IBD 2009-2015	N = 238
Ø – Procedure time (mints.)	105 (65-295)
Ileo-Colic resection	154
Hemicolectomy	41
Subtotal colectomy	32
PC with IPAA	11
Bowel gas movement (days)	3,1 (1-5)
Bowel stool movement (days)	4,6 (2-6)
Complications	11 (3,2 %)
Hospital stay (days)	5,2 (4-16)

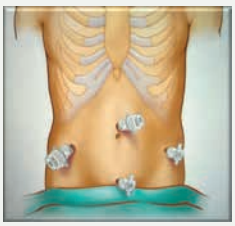

Dis Colon Rectum 2014; 57: 1349–1357
Subtotal Colectomy in Severe Ulcerative and Crohn's Colitis: What Benefit Does the Laparoscopic Approach Confer?


World Journal of Gastrointestinal Surgery
Risk factors and implications of anastomotic complications after surgery for Crohn's disease

- Laparoscopic surgery in IBD is safe and feasible with minimal injury of the abdominal wall, organs and tissues.
- It offers both cosmetic advantage and some short term advantage, such as a possible reduction in perioperative complications.
- Long term benefits include fewer incisional hernias and fewer adhesions with a significant impact on female fertility in UC patients.

BENEFITES OF MIS IN IBD

- Important factor for young-adult population
  - Small incisions with less pain and improved cosmetic status
  - More rapid return to full functional status like work and school
  - Minimal injury of the abdominal wall
    - No limits for sports



CONCLUSION

- Miniinvasive laparoscopic colorectal surgery for IBD is becoming the standard worldwide because of superior short and long-term outcomes when performed by experienced surgeons in referral centers with specialized teams.
- MIS has not influence on the basic character and course of the IBD

Lesperance K: National Trends and Outcomes for the Surgical Therapy of Ileocolic Crohn's Disease: A Population-based Analysis for Laparoscopic v.s. Open Aproaches. J Gastrointest Surg, 2009,13:1251-1259.

Cary BA. Laparoscopic surgery for Crohn disease: A brief review of literature. Clin Colon Rectal Surg 2013; 26: 122-127.

ENDOSCOPIC SURVEILLANCE OF COLORECTAL CARCINOMA AND DYSPLASIA IN IBD PATIENTS

Vito ANNESE

Gastroenterology Unit SOD2, Careggi University Hospital, Florence; Italy

People with long-standing ulcerative colitis (UC) and Crohn's disease (CD) colitis have a higher risk of developing colorectal cancer (CRC) than the general population. Initial estimates based on the meta-analysis by Eaden *et al.* (Gut 2001) of 116 studies including population-based and hospital-based cohorts found an overall prevalence of CRC to be 3.7%. However the magnitude of risk in recent population-based studies appears smaller than in earlier studies. Indeed a more recent meta-analysis of population-based cohorts (Tess *et al.*, CGH 2012) concluded that UC increases the risk of CRC 2.4-fold. The reasons for the apparent reduced risk of CRC over time is unclear but may include early study selection bias, improved control of mucosal inflammation, more extensive use of 5-ASA compounds, the implementation of surveillance programmes and timely colectomy.

Several independent factors affect the magnitude of CRC risk. The colonic extent of mucosal inflammation is the best established. Risk is highest in those with pancolitis with a SIR ranging from 2.8 for left-sided colitis to 5.6 for pancolitis (Annese *et al.*, JCC 2013). In addition, patients with severe inflammation, patients with colitis-associated primary sclerosing cholangitis (PSC), and patients with a family history of CRC may have a particularly increased risk.

The endoscopy has a critical role in surveillance of colorectal cancer and detection of dysplasia. Surveillance colonoscopy programmes aim to reduce morbidity and mortality due to CRC by detecting cancer at an earlier stage with better prognosis or by detecting and resecting dysplasia, thus reducing CRC incidence. Screening colonoscopy should be offered at estimated 8 years after the onset of symptoms to all patients to reassess disease extent. Subsequently, surveillance should be performed in all patients apart from those with proctitis or Crohn's colitis involving only one segment of colorectum. So far there is no clear evidence for surveillance intervals, therefore intervals are individualized based on risk stratification as high, intermediate or low, based on known risk factors. In this context the colonoscopy is traditionally coupled with histology, with the need of multiple biopsies. This is suboptimal for dysplasia detection and time consuming for either endoscopists or pathologists. The utilization of chromoendoscopy, possibly combined with magnification, is actually considered the "gold standard", given the adequate diffusion of the methodology and the opportunity to perform targeted rather than random biopsies. In contrast, so far, the techniques of so called virtual or optical chromoendoscopy, although more operator friendly, have not proven to be comparable to chromoendoscopy with vital colorants. However, technology is on progress and several comparative trials underway. Finally, future development and diffusion of confocal endomicroscopy or endocytoscopy could prove further advantage including the need of less biopsies or avoid histology. However, possible medico-legal consequences should be taken into account, and cost/effectiveness, learning curve and length of procedure are still an issue.

When dysplasia is found should be confirmed by an independent experienced pathologist. A visible lesion with dysplasia should be completely resected by an experienced endoscopist, irrespective of the grade of dysplasia or the localisation, provided that dysplasia is absent in surrounding mucosa and rest of the colon. If endoscopic resection is not possible or if dysplasia is found in the surrounding flat mucosa, proctocolectomy should be recommended (Annese *et al.*, JCC 2013).

Annese V. Endoscopic surveillance of colorectal carcinoma and dysplasia in IBD patients. In: *11th International Symposium of Gastroenterology, Saint Petersburg, Russia, 12–14 May 2016*. [online].
Available from URL: http://www.promedcs.eu/sites/default/files/abstractbook_2016.pdf

11th International Symposium of GASTROENTEROLOGY
12–14 May 2016, Saint Petersburg, Russia

ENDOSCOPIC SURVEILLANCE OF COLORECTAL CARCINOMA AND DYSPLASIA IN IBD PATIENTS

Vito ANNESE

AOU Careggi University Hospital,
Florence, ITALY

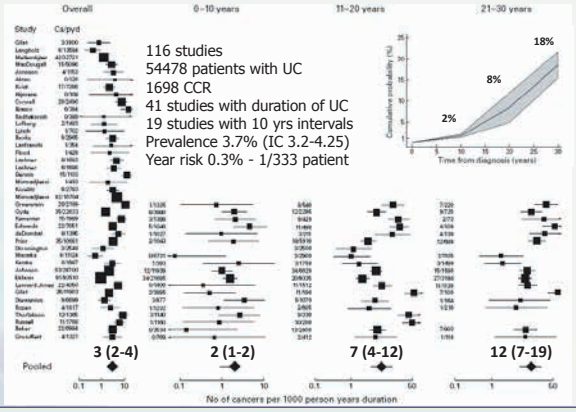
QUESTIONS TO BE ANSWERED

1. Do we need to screen IBD patients more intensely for colorectal cancer and dysplasia ?
2. Has every IBD patient the same risk ?
3. How do we increase detection ? Do we need advanced imaging ?
4. How dysplasia should be managed ?

QUESTIONS TO BE ANSWERED

1. **Do we need to screen IBD patients more intensely for colorectal cancer and dysplasia?**
2. Has every IBD patient the same risk ?
3. How do we increase detection ? Do we need advanced imaging ?
4. How dysplasia should be managed ?

Meta-analysis - Eaden JA et al. - GUT 2001;48:526-535

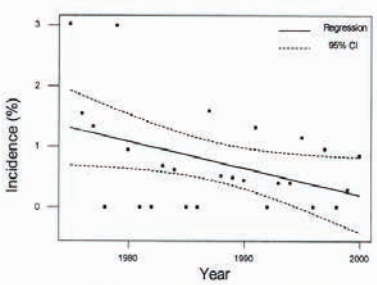


Thirty-Year Analysis of a Colonoscopic Surveillance Program for Neoplasia in Ulcerative Colitis

GASTROENTEROLOGY 2006;130:1030–1038

MATTHEW D. RUTTER,*,† BRIAN P. SAUNDERS,† KAY H. WILKINSON,† STEVE RUMBLES,† GILLIAN SCHOFIELD,† MICHAEL A. KAMM,† CHRISTOPHER B. WILLIAMS,† ASHLEY B. PRICE,† IAN C. TALBOT,‡ and ALASTAIR FORBES†

*Department of Gastroenterology, University Hospital of North Tees, Stockton-on-Tees, Teesside, England; and ‡St Mark's Hospital, Harrow, London, England



Regression plot of CRC incidence over time.

600 patients in F-up
dal 1971 al 2001
5932 patient/year of F-up

CANCER RISK IN UC

British 30 year prospective data

- 600 UC pt
- Incidence of neoplasia
  - 1.5% 10 years
  - 7.7% 20 years
  - 15.8% 30 years
  - 22.7 % 40 years
  - 27.5 % 45 years
- Incidence of CRC
  - 2.5 % 20 years
  - 7.6 % 30 years
  - 10.8% 40 years

Rutter et al GASTROENTEROLOGY 2006;130:1030–1038

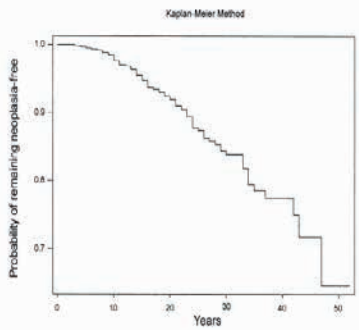


Figure 1. Time from UC onset to dysplasia/cancer.

CANCER RISK IN UC

British 30 year prospective data

- 600 UC pt
- Incidence of neoplasia
  - 1.5% 10 years
  - 7.7% 20 years
  - 15.8% 30 years
  - 22.7 % 40 years
  - 27.5 % 45 years
- Incidence of CRC
  - 2.5 % 20 years
  - 7.6 % 30 years
  - 10.8% 40 years

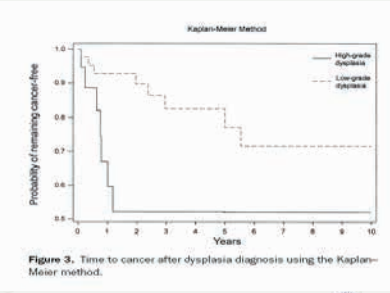


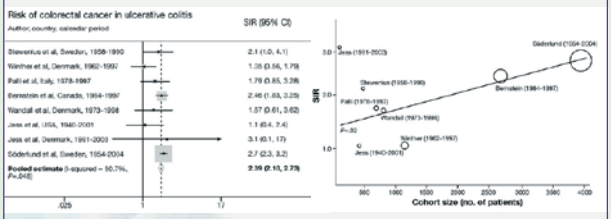
Figure 3. Time to cancer after dysplasia diagnosis using the Kaplan–Meier method.

Rutter et al GASTROENTEROLOGY 2006;130:1030–1038

Risk of Colorectal Cancer in Patients With Ulcerative Colitis: A Meta-Analysis of Population-Based Cohort Studies

CLINICAL GASTROENTEROLOGY AND HEPATOLOGY 2012;xx:xxx

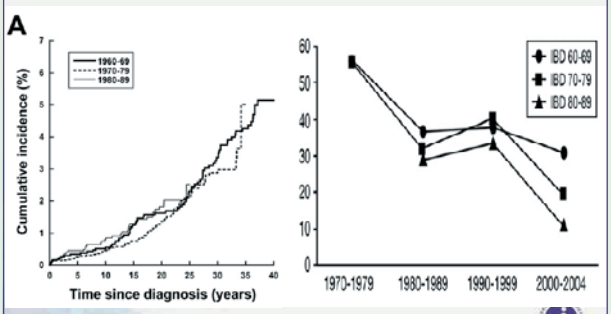
TINE JESS,* CHRISTINE RUNGOE,* and LAURENT PEYRIN-BIROULET‡



8 studies, F-up 7-24 aa, colectomies 5-31%
Total SIR = 2.4 (CI 2.1-2.7)
Male = 2.6 (CI 2.2-3); Female = 1.9 (CI 1.5-2.3)
Age < 40 = 8.6 (CI 3.8-19.5)
Extensive colitis = 4.8 (CI 3.9-5.9)

ROLE OF SURVEILLANCE

Risk for CRC **Mortality from CRC / 100.000 pers years**



N=7607

Soderlund et al GASTROENTEROLOGY 2009;136:1561–1567

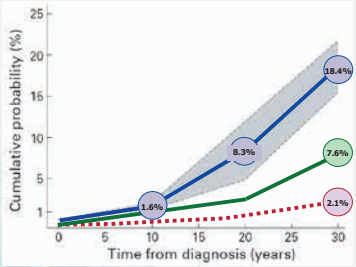
QUESTIONS TO BE ANSWERED

1. **Do we need to screen IBD patients more intensely for colorectal cancer and dysplasia?** YES
2. Has every IBD patient the same risk ?
3. How do we increase detection ? Do we need advanced imaging ?
4. How dysplasia should be managed ?

QUESTIONS TO BE ANSWERED

1. Do we need to screen IBD patients more intensely for colorectal cancer and dysplasia ?
2. **Has every IBD patient the same risk ?**
3. How do we increase detection ? Do we need advanced imaging ?
4. How dysplasia should be managed ?

RISK FACTORS FOR CRC



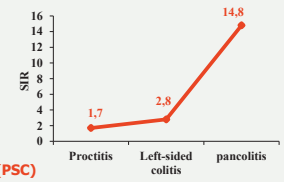
Eaden, M-A 2001

Rutter, 2006 (St Marks)

Copenhagen Co (population based)

RISK FACTORS FOR CRC

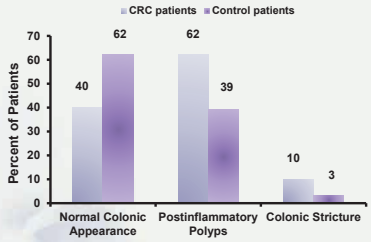
- ✓ Disease duration
- ✓ Extend of inflammation



- ✓ **primary sclerosing cholangitis (PSC)**
- ✓ Young age at disease onset (<30ys)
- ✓ Familiy history of CRC
- ✓ Post-inflammatory polyps
- ✓ Active inflammation (also histologically)

Ekbom A, New Engl J Med 1990

RISK FACTORS FOR CRC



OR 0.38 [0.19, 0.73]	OR 2.29 [1.28, 4.11]	OR 4.62 [1.03, 20.8]
P=.003	P=.005	P=.05

Rutter MD et al. *Gut.* 2004;53:1813.

ECCO Statement 2A

Patients with IBD are at increased risk of developing colorectal cancer [CRC] [EL 1] which, in the case of ulcerative colitis [UC], varies with the extent and duration of the disease [EL 1], family history of CRC, and the presence/absence of primary sclerosing cholangitis [PSC] [EL 1].
Over the past 35 years the risk of dying from CRC has decreased [EL 1]

Annese V et al. JCC 2015, 945–965

QUESTIONS TO BE ANSWERED

1. Do we need to screen IBD patients more intensely for colorectal cancer and dysplasia ?
2. **Has every IBD patient the same risk ?**
   NO – Surveillance should be tailored
3. How do we increase detection ? Do we need advanced imaging ?
4. How dysplasia should be managed ?

CRC Screening in IBD-colitis

SCREENING COLONOSCOPY
8 years after the onset of symptoms
to all patients to reassess disease extent

SURVEILLANCE

HIGH RISK FACTORS	INTERMEDIATE RISK FACTORS	LOW RISK FACTORS
stricture or dysplasia detected within the past 5 years, PSC,extensive colitis with severe active inflammation,family history of CRC in a first degree relative at less than 50 years	extensive colitis with mild or moderate active inflammation, post-inflammatory polyps, family history of CRC in a first degree relative at 50 years and above	Patients with neither intermediate nor high risk features, i.e. left side colitis, Crohn's colitis < 50% colon, extensive colitis with no inflammation
Every year	Every 2-3 years	Every 5 years

Annese V et al. JCC 2013:7: 982–1018

QUESTIONS TO BE ANSWERED

1. Do we need to screen IBD patients more intensely for colorectal cancer ?
2. Has every IBD patient the same risk ?
3. **How do we increase detection ? Do we need advanced imaging ?**
4. How dysplasia shoudl be managed ?

STANDARD BIOPSY PROTOCOL

Surveillance endoscopy
- No or mild inflammation
- 4 random quadrant biopsies / 10 cm
- + visible lesions

Accuracy for detection neoplasia
- 90 % for 33 biopsies
- 95 % for 56 biopsies

Rubin et al Gastroenterology 1992;103:1611
Connell et al Gastroenterology 1994;107:934

STANDARD BIOPSY PROTOCOL

Adherence problem

Country	Adherence
Netherlands	25%
UK	57% take < 10 biopsies/pt
New Zealand	50% take < 17 biopsies/pt
Germany	9% adh; 50% < 10 biopsies

Obrador et al Aliment Phar Ther 2006;24:56
Eaden et al GIE 2000;51:123
Gearry et al Dis Colon Rectum 2004;47:314
Kaltz et al Z. Gastroenterol 2007;45:325

STANDARD BIOPSY PROTOCOL

1010 colonoscopies in 475 patients (1998-2008)

466 surveillance colonoscopies in 166 patients

11772 random biopsies

24 (0.2%) biopsies with neoplasia
- 23 LGIN
- 1 HGIN

432 targeted (suspicious lesions)

101 (23%) neoplastic :
- 29 LGIN
- 56 unspecified
- 13 HGIN
- 3 cancer

Van den Broek F et al Am J Gastroenterol. 2014 May;109(5):715-22

IBD-Colitis

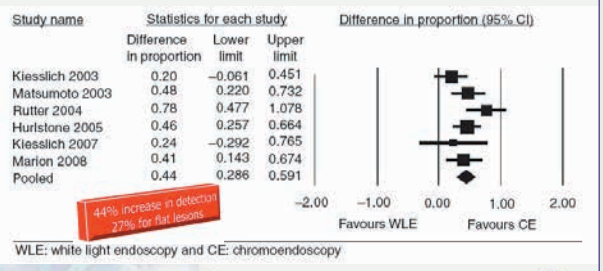
CHROMO-ENDOSCOPY IN UC

	N	Method	Increase in diagnostic yield
Kiesslich et al	165	Methylene Blue	3-fold/lesion
Matsumoto et al	57	Indigo Carmine	2-fold increase in sensitivity
Rutter et al	100	Indigo Carmine	4-fold/lesion
Hurlstone et al	324	Indigo Carmine	4-fold/lesion
Kiesslich et al	161	Methylene Blue+CLE	4.75-fold/lesion
Marion et al	115	Methylene Blue	1.5 fold
Hlavaty et al	30	Indigo Carmine 0.4%	12 vs 0 pt for random X 2 vs targeted WL

Kiesslich et al, Gastroenterology 2003;124(4):880 ; Rutter et al Gut 2004;53(2):256; Hurlstone et al Gastroenterology 2004;126(1):376; Kiesslich et al Gastroenterology 2007;132:874–882.
Marion et al Am J Gastroenterol 2008; Hlavaty et al Eur J Gastro Hep 2011

IBD-COLITIS

Meta-analysis of chromo-endoscopy in UC screening



WLE: white light endoscopy and CE: chromoendoscopy

Subramanian et al Aliment Pharmacol Ther 2011; 33: 304–312

SURFACE GUIDELINES

Strict patient selection
- ✓ Histologically confirmed IBD colitis at least 8 years, in clinical remission.
- ✓ Avoid patients with active disease

Unmask the mucosal surface
- ✓ Bowel prep; remove mucus and fluid

Reduce peristaltic waves
- ✓ If necessary use spasmolytic agent on extubation

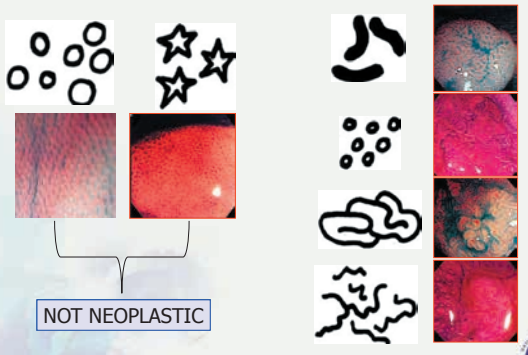
Full length staining of the colon (pan-chromocolonoscopy)

Augmented detection with dyes
- ✓ Indigo 0,4% of methylene blue 0,1%

Crypt architecture analysis
- ✓ Pit pattern assessment

Endoscopic targeted biopsies
- ✓ Targeted biopsies of all mucosal alterations, in particular circumscribed lesions

KUDO'S PIT PATTERN CLASSIFICATION



Kudo et al : J Clin Pathol 1994; 47: 880
Hurlstone et al British Journal of Surgery 2002, 89, 272

DIAGNOSTIC ACCURACY

Diagnostic accuracy	Modality	Absence pit pattern I/II	Endoscopic appearance
Sensitivity	overall	77%	77%
	CE	88%	88%
	NBI	60%	60%
Specificity	overall	68%	69%
	CE	63%	59%
	NBI	74%	76%
NPV	overall	88%	90%
	CE	89%	91%
	NBI	89%	89%
PPV	overall	46%	48%
	CE	**57%***	**55%***
	NBI	**35%***	**38%***
Accuracy	overall	70%	72%
	CE	73%	71%
Bisschops et al DDW 2013	NBI	71%	73%

QUESTIONS TO BE ANSWERED

1. Do we need to screen IBD patients more intensely for colorectal cancer ?
2. Has every IBD patient the same risk ?
3. **How do we increase detection ? Do we need advanced imaging ?** **YES**
4. How dysplasia should be managed ?

ECCO Statement 13G

Pan-colonic methylene blue or indigo carmine chromoendoscopy should be performed during surveillance colonoscopy, with targeted biopsies of any visible lesion [EL2].

If appropriate expertise for chromoendoscopy is not available, random biopsies (4 every 10 cm) should be performed [EL3]; however this is inferior to chromoendoscopy in the detection rate of neoplastic lesions [EL2]

[Voting results: 100% agreement]

Annese V et al. JCC 2013,7;982–1018

ECCO Statement 13H

Other image enhancement techniques such as narrow band imaging or autofluorescence have not been convincingly demonstrated to be superior to white light endoscopy or chromoendoscopy in the detection of neoplastic lesions, thus they cannot currently be recommended for colitis surveillance [EL2]

[Voting results: 93% agreement].

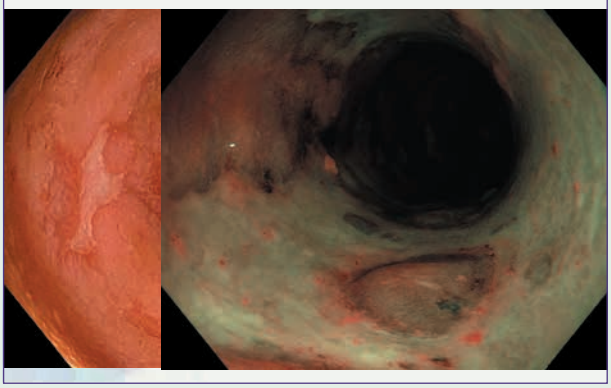
Annese V et al. JCC 2013,7;982–1018

QUESTIONS TO BE ANSWERED

1. Do we need to screen IBD patients more intensely for colorectal cancer ?
2. Has every IBD patient the same risk ?
3. How do we increase detection ? Do we need advanced imaging ?
4. **How dysplasia should be managed ?**

HOW TO MANAGE DYSPLASIA ?

The key for endoscopic treatment is to have a VISIBLE dysplasia



HOW TO MANAGE DYSPLASIA ?

ECCO Statement 13L

- Where dysplasia of any grade is found without an associated endoscopically visible lesion, urgent repeat chromoendoscopy should be performed by an experienced endoscopist to determine whether a well circumscribed lesion exists and to assess for synchronous dysplasia [EL5]
- [Voting results: 100% agreement].

Annese V et al. JCC 2013; 7, 982–1018

HOW TO MANAGE DYSPLASIA ?

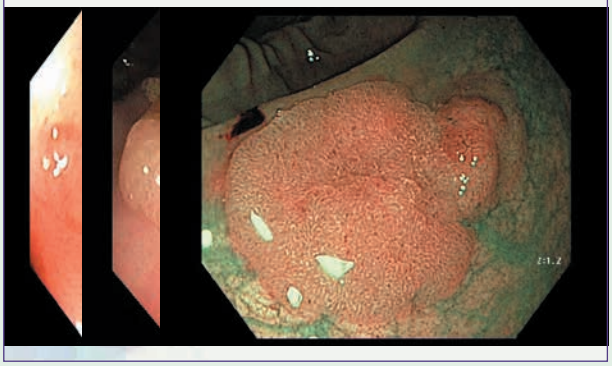
ECCO Statement 13K

- A visible lesion with dysplasia should be completely resected by an experienced endoscopist, irrespective of the grade of dysplasia or the localisation relative to the inflamed mucosal areas [EL1].
- This applies also for sporadic adenomas in the context of colitis.
- In the absence of dysplasia in the surrounding mucosa, ongoing meticulous colonoscopic surveillance is appropriate [EL1].
- [Voting results: 100% agreement].

Annese V et al. JCC 2013; 7, 982–1018

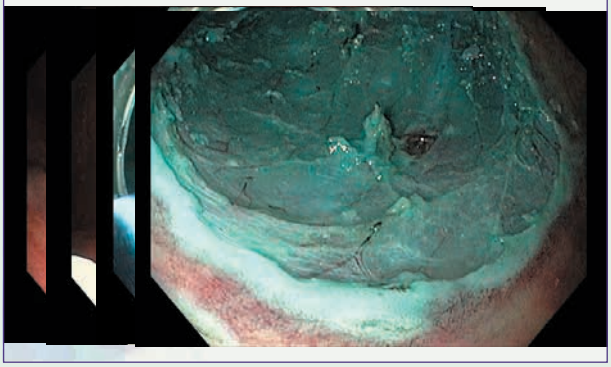
CASE 1

47 yrs, pancolitis, 15 yrs duration of disease under 5-ASA
Negative CRC familiy history, LGD only on the lesion



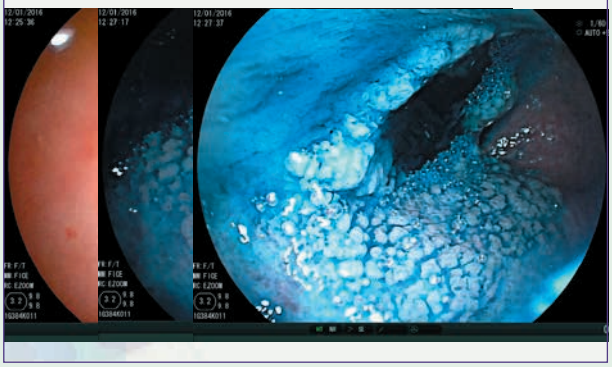
CASE 1

EMR = 25 mm size, confirmed LGD



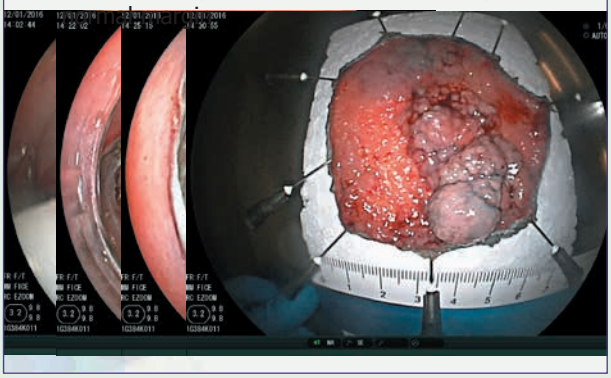
CASE 2

55 yrs, left side colitis since 20 yrs, large LST with LGD

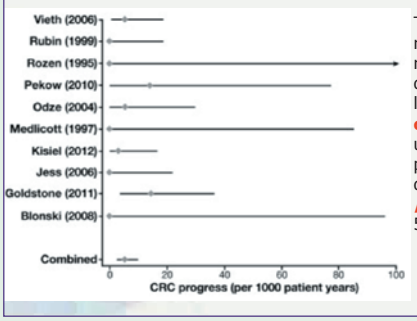


CASE 2

ESD 6 x 7 cm, villous adenoma with LGD,



A META-ANALYSIS OF CANCER RISK AFTER RESECTION OF POLYPOID DYSPLASIA



The pooled incidence rate of cancer after resection of polipoid dysplasia in patients with longstanding UC is **5.3 cases /1000yrs** follow-up (CI 2.7-10.1), but a pooled rate of any dysplasia of **65 cases /1000yrs** follow-up (CI 54-78)

Wanders LK et al, CGH 2014

DEFINITE INDICATIONS FOR SURGERY

- Endoscopically unresectable lesions
- High grade dysplasia without visible lesions
- Multifocal LGD
- Combination of risk factors (e.g. PSC, multifocal dysplasia)
- Dysplasia in multiple post-inflammatory polyps

QUESTIONS TO BE ANSWERED

1. Do we need to screen IBD patients more intensely for colorectal cancer ?
2. Has every IBD patient the same risk ?
3. How do we increase detection ? Do we need advanced imaging ?
4. **How dysplasia should be managed ?**
   YES WE CAN

Take home notes for Dysplasia

Endoscopically visible and resectable lesion:

- Remove the lesion
- Take biosies from surrounding mucosa
- Tattoo lesions
- Inspection of site of resection at 3 months

- **Endoscopically invisible dysplasia:**
- Review of histopathology by expert pathologist
- Repeat endoscopy by experienced endoscopist with HD scope and chromoendoscopy
- Take-4-quadrant biopsies
- Discuss management with patient

Grazie per l'attenzione

спасибо за внимание

FUNCTIONAL GI DISORDERS AND IBD DEBUT (CLINICAL CASES)

Sergej VYALOV

GMS Clinic, Moscow; Russian Federation

The incidence of IBD increases in recent years. At the same time, the incidence of IBS also increases. It is possible to conclude that IBS and IBD are multifactorial diseases. It is simple to appoint the key role of environmental factors in the incidence increase. We should also pay attention to colon health in patients with IBS and their potential risk of IBD development.

Modern medicine is hi-tech medicine: receptors, antibodies, TNF, regulation, genes expression, etc. Today we use advances in molecular and genetic medicine, we may activate or inhibit different receptors. Modern advances require their application in practice. Therefore, we examine the "micro" causes of disease only. On the contrary, it is extremely difficult to quantitatively measure the level of stress or level of the environmental factors. So they go out from our sight.

Usually patients with IBD visited the doctor with an already developed full picture of the disease. But it is necessary some time for the formation pattern of the disease. In many cases we treat the single episodes of disease in the patient. And then, for unknown reasons, IBD is occurs. What leads from the healthy patient to the patient with Crohn's disease? What leads from the healthy patient to the patient with ulcerative colitis?

At the early stages (preliminary stages) of the disease, patients are out of doctor's sight. There is the patient with infectious diarrhea. He was treated successfully. He had left the hospital and returned in a couple of years. Finally, we find out now that he suffer from ulcerative colitis.

It is very difficult task organize a long study, the purpose of which is the monitoring and estimation of all factors that can lead to IBD. The experience of our clinic allows us to follow the patient history for a long time. I will try to demonstrate this transformation from IBS to IBD with several examples.

The patients in preliminary stage of IBD are observed with IBS diagnosis. He did not repeat the colonoscopy at least once or twice in one or two years. He was calm, because doctors did not find anything. Patients with experience of some years of IBS may have colitis under the mask of the symptoms. In certain cases, treatment of IBS in patients with IBD may hide or modify clinical picture and complicate the diagnosis.

"The road" goes to IBD from IBS: IBS – the absence of pathology on colonoscopy. The next step is the development of non-specific non-infectious colitis, which did not satisfy under the IBD criteria (UC or CD). In this case, there no standards of treatment or other recommendations. After the time we will identify IBD on follow-up colonoscopy.

Conclusions. It is necessary to provide a continuous monitoring of patients with IBS and regular or periodically colonoscopy for early detection of IBD and early treatment.

+7 (926) 585-16-92
svialov@mail.ru
www.vyalov.com

Vyalov S. Functional GI disorders and IBD debut (clinical cases). In: *11th International Symposium of Gastroenterology, Saint Petersburg, Russia, 12–14 May 2016*. [online].
Available from URL: http://www.promedcs.eu/sites/default/files/abstractbook_2016.pdf

11th International Symposium of GASTROENTEROLOGY
12–14 May 2016, Saint Petersburg, Russia

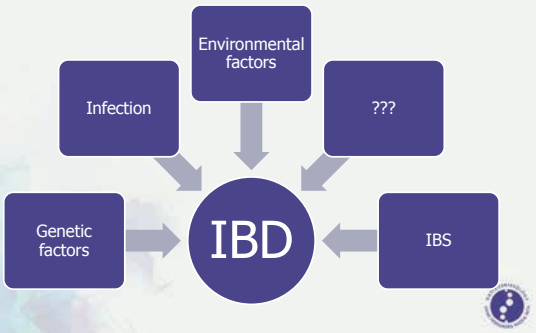
FUNCTIONAL GI DISORDERS AND IBD DEBUT (CLINICAL CASES)

Vyalov S. Sergey

Russian Peoples' Friendship University, GP department
RUSSIAN FEDERATION

CONFLICTS OF INTEREST

- No conflicts

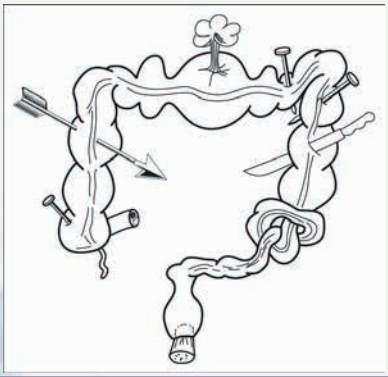


FUNCTIONAL GI DISORDERS

FD

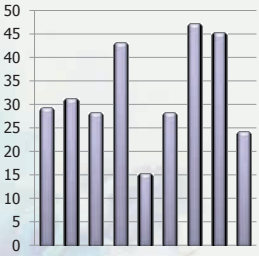
IBS

IBS SYMPTOMS

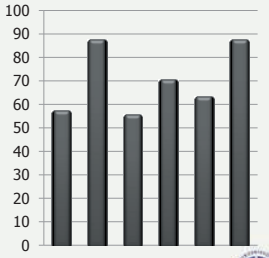


FGID «OVERLAP»

IBS in FD patients, %



FD in IBS patients, %

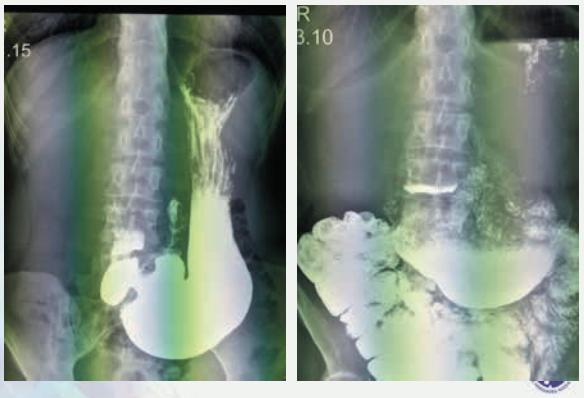


Ivashkin VT, Sheptulin AA, Kiprianis VA. FD: short practice guideline, 2011

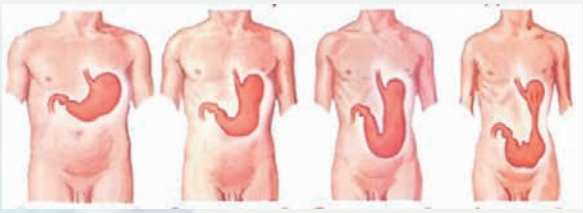
CASE #6

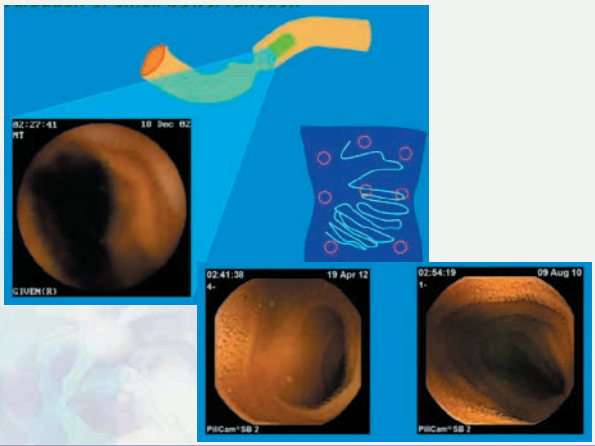
- Woman, 45 y.o.
- IBS with predominant pain

- Feel sick during 9 months
- Irregular pain, most common in left abdomen
- No response on spasmolytic, probiotic
- Colonoscopy – w/o changes



WHERE IS MY STOMACH?!





CASE #3

- Man, 42 y.o.
- IBS with pain, diarrhea, constipation

- Feel sick during 4 years
- Irregular symptoms
- CBD, Blood biochemistry, Urine tests, Stool tests, Anti-bodies, USE, Gastro, Colono, CT, MRI – w/o changes
- Patient was treated by many gastroenterologist and himself

GEMC
GROUP OF COMPANIES EUROPEAN MEDICAL CENTER

SMALL INTESTINE EXAMINATION RECORD VIDEO CAPSULE ENDOSCOPY (VCE) MIROCAM model: MC1000-W (SN:MC1B5T120523069)
CONCLUSION: Moderate endoenteritis with hemorrhagic component. Helminth infestation of the intestine (ascariasis)

Small intestine	Transit disorder is not defined	In the jejunum and ileum: wide lumen, no narrowing is detected, dull mucous membrane, with foci of hyperemia, punctate hemorrhages, velvety, the villi are structured, edematous, accentuated vascular pattern, maintained along the whole length. Angiectasis is not detected. The test for blood is positive. No intraluminal formations are visualized. No indirect evidence of submucosal mass is detected. In the distal ileum a large number of Nematodes is visualized (ascarids).	
Large intestine	Passage to the large intestine after 6 hours 50 minutes.	Helminths (ascarids) in the head of blind colon.	

CONCLUSION:
Moderate endoenteritis with hemorrhagic component Helminth infestation of the intestine (ascariasis).

There are people in whose lives God,
There are people in whom the devil lives,
There are people that only live worms
Faina Ranevskaya

CASE #1

- Woman, 33 y.o.
- IBS with diarrhea

- Bowel movement 4-7 times a day, liquid, sometimes with blood
- Bloating, abdominal distention, pain in underbelly
- Feel sick during 3 months w/o improvement
- No response on spasmolytic and probiotic

PROTOCOL OF ENDOSCOPIC EXAMINATION

Date of examination: 27.08.2014.
Department: Day patient facility
Name: XXX
Age: DOB 1981
Medical history No.: 11989 PLT

COLONOSCOPY

Video colonoscope Olympus Evis Lucera CF-FH260AZL was input till the middle third of the sigmoid colon
Further the colon forms a sharp bend which was not possible to pass through due to occurrence of pronounced pain in the patient
There is small amount of liquid in the lumen of the colon. The sigmoid colon forms additional loops
The mucous membrane of the large intestine in the examined areas is pink, smooth and luculent
The vascular pattern is clear, regular. The folds of mucous are of average size, elastic. The lumen of the intestine is not deformed
The tone of the intestine is normal

CONCLUSION:
In the examined areas on the side of large intestine no organic pathology is revealed

Doctor: Kirova M.B. [signature] | Nurse: Romanova M.I.

Врач: Кирова М.Б. | М/с: Романова М.И.

ГУТА КЛИНИК

Autonomous Non-Profit Organization Guta Clinic
2 Fadeeva St., 127006 Moscow, (495) 545-40-40

Video colonoscopy

Patient: XXX, medical history No. 60597, completed years: 33.
Doctor – Endoscopist: Gorkovtsov Andrey Viktorovich
Date, time of attendance: 22.09.2014, 12:47:48

+ 3 weeks

REF NEX0222-G
LOT 110302-2 ENDO-FLEX

Examination:

The colonoscope was inserted into the head of blind colon. The head is well straightened with air
In its bottom the appendix opening is clearly visualized. Its opening is oval, peristaltic, free
The appendix plate is smooth, elastic. Ileococcal valve is lip-shaped, oriented in the lumen of the head, caudal
The lumen and tone of the intestine are maintained along the whole length. The mucous membrane is pink, the vascular pattern is clear
In the rectum at a distance of 8-10 cm from the anal ring on all the walls the mucous membrane is with multiple "stamped" defects of round and oval shape – aphthous lesions up to 0.3 cm in diameter with hyperemia crowns, haemorrhagic intramural lesions of perifocal defects. Biopsy No.1-2. The vascular pattern is blurry, with mucus in the lumen

Conclusion:

Aphthous hemorrhagic proctitis, rule out nonspecific ulcerative colitis (discrete form with rectal lesion, acute stage, the exacerbation phase)

Recommendations:

1. Control of biopsy after 10 working days, tel. 545 4040.
2. Consultation and monitoring by the proctologist, gastroenterologist.

Doctor – Endoscopist:
Gorkovtsov Andrey Viktorovich [signature]

CASE #4

- IBS with pain, diarrhea
- Feel sick during 4 years
- Irregular pain w/o localization
- Improvement on spasmolytic
- Regular stool bacteriology – recurrent pathogens, as consequence – antibiotics

GEMC
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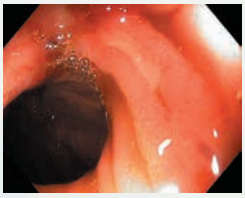
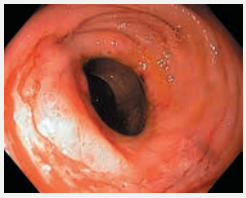
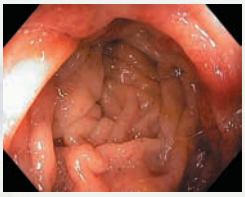
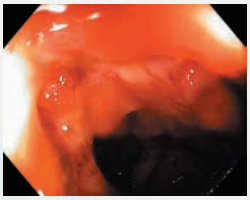
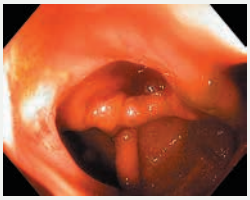
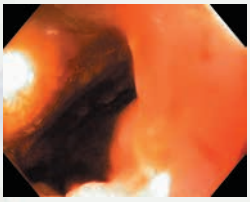
Company: SCH OUT / Поликлиника Щелкина — Lab.Visit: 10188874

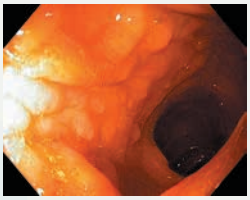
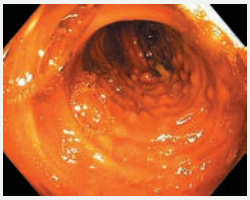
DATE: 18.09.2014
TIME: 16:08
DR : VITALOV Sergey
PATIENT: [redacted]
AGE:
DOB:

MICROBIO/PARASITOLOGY/PATO

Constituent	Results	Units	Limits
Specimen	faeces		
TOTAL PROPERTIS			
Color	rusty-brown		
Form	made out nonformalized		
Consistency	liquid		
Mucus	not many		
Blood	Detected		
Debris	abs		
CHEMICAL INVESTIGATION			
Reaction (pH)	weakly acid		
Occult blood	Positive		
MICROSCOPICAL INVESTIGATION			
Mucus	abs		
Epithelium	abs		
Leukocyte	many		
Erythrocytes	many		
Yeast	abs		
Protozoa	abs		
Parasite eggs	abs		
Calprotectin in stool	↑ 6840.0	ug/g	(<50.0)

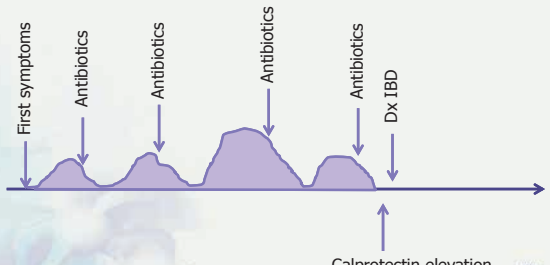
GEMC
GROUP OF COMPANIES EUROPEAN MEDICAL CENTER

Company: SCH OUT / Поликлиника Щелкина — Lab.Visit: 10208599

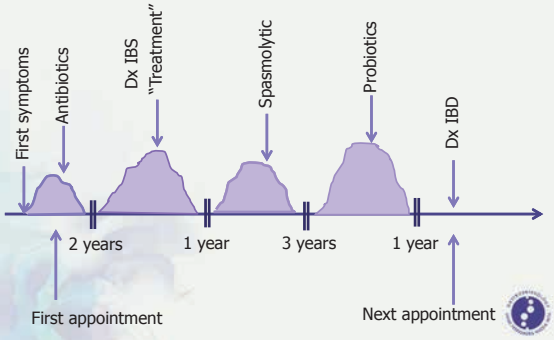
DATE: 25.11.2014
TIME: 16:38
DR : VITALOV Sergey
PATIENT: [redacted]
AGE:
DOB:

MICRODIO/PARASITOLOGY/PATO

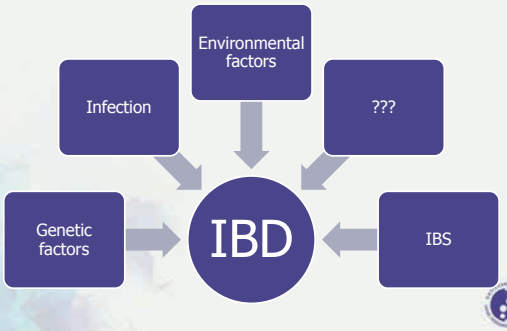
Constituent	Results	Units	Limits
Specimen	faeces		
TOTAL PROPERTIS			
Color	brown		
Form	formed		
Consistency	consistency		
Mucus	not many		
Blood	Not detected		
Debris	not many		
CHEMICAL INVESTIGATION			
Reaction (pH)	neutral		
Occult blood	Weak positive		
Mucus	not many		
Epithelium	abs		
Leukocyte	abs		
Erythrocytes	abs		
Yeast	abs		
Protozoa	abs		
Parasite eggs	abs		
Calprotectin in stool	↑ 9100.0	ug/g	(<50.0)



TYPICAL IBS->IBD PATIENT



MULTIFACTORIAL CONCEPT OF IBD



2.2 Diagnosis

ECCO statement 2B

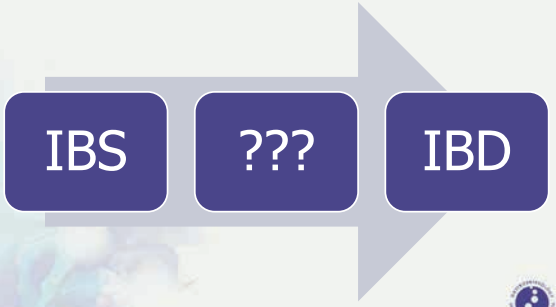
A single gold standard for the diagnosis of CD is not available. The diagnosis is confirmed by clinical evaluation and a combination of endoscopic, histological, radiological, and/or biochemical investigations. Genetic testing is currently not recommended for routine diagnosis or management of CD. [EL5, RG D].

3.3.3 Diagnosis

ECCO statement 3E

A gold standard for the diagnosis of ulcerative colitis is not available. The diagnosis should be established by a combination of medical history, clinical evaluation, and typical endoscopic and histological findings. An infective cause should be excluded. Where there is doubt about the diagnosis, endoscopic and histological confirmation is necessary after an interval [EL5, RG D]

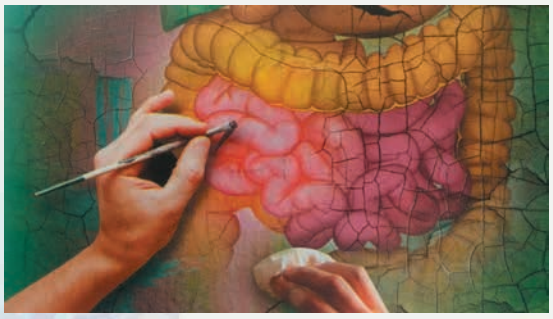
IBS PITFALL



IBS	• Rome III • FGID criteria
non-IBS and non-IBD	• "Chronic colitis" • Simply inflammation
IBD	• UC or CD criteria • Other criteria

HOME MESSAGE

- It is necessary to provide a continuous monitoring of patients with IBS and regular or periodically colonoscopy for early detection of IBD and early treatment



QUESTIONS OF DIAGNOSTICS AND TREATMENT OF DIFFERENT FORMS OF GERD

Vladimir I. SIMANENKOV

Northwestern State Medical University named after I. I. Mechnikov, Saint Petersburg; Russian Federation

Currently, gastroesophageal reflux disease (GERD) is the number one among all the diseases of the upper gastrointestinal tract (GIT).

Major epidemiological studies show that 10–20% of Western population (Dent *et al*., 2005) and 13.3% of Russian population (Lazebnik, 2009) suffer from gastroesophageal reflux disease (GERD).

It is well know that GERD is based on disorders of the motor-evacuation function of the gastroesophageal area which lead to regularly repeated gastric and/or duodenal content refluxes into the esophagus. It causes the development of a few specific clinical symptoms and morphological changes of the esophageal mucosa. The main goals of the treatment of GERD are quick control of clinical symptoms of the disease, complete repair of mucosal erosions and ulcers, prevention and liquidation of complications, and improvement of the quality of life of the patients. At present, proton pump inhibitors (PPIs) are still the basic medication of therapy for GERD. However, despite their high efficacy and safety, it is sometimes very hard to obtain the intended effect. The last two decades, more and more attention is given to the study of pathogenesis, diagnostics and treatment aspects of GERD together with duodenogastroesophageal reflux (DGER). The interest to this issue is due to the frequent association of pathological biliary refluxes with severe forms of GERD and their possible role as an important forming agent of clinical resistance to PPIs.

Study objective. To study clinical and pathogenic aspects of non-acid GERDs and to evaluate effect of monotherapy and combination therapy on the course of the pathology.

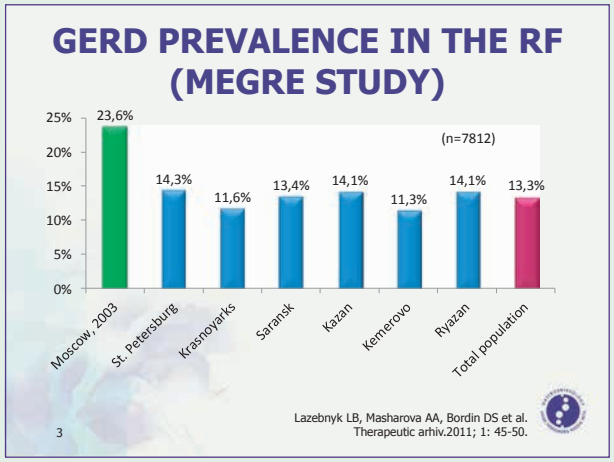
Materials and methods. The study included 46 patients with non-acid GERDs. The follow-up period took 6 weeks. The patients were divided into 2 groups: weakly acidic GER and weakly alkaline GER. Then, randomization was carried out in each group, this way 4 groups were formed: group 1 – patients with weakly acidic gastroesophageal reflux (GER) receiving monotherapy by rabeprazole in the dose of 20 mg daily (12 patients), group 2 – patients with weakly acidic GER receiving combination therapy with rabeprazole 20 mg and itopride (15 patients), group 3 – patients with weakly alkaline GER receiving monotherapy by UDCA (8 patients), and group 4 – patients with weakly alkaline GER receiving combination therapy by UDCA and itopride (11 patients). Follow-up evaluation of clinical symptoms of the disease, social and psychological status, endoscopic manifestations of the upper GIT mucosa, *H. pylori* contamination, histological changes of the esophageal and gastric mucosa, and daily impedance-pH monitoring results was performed.

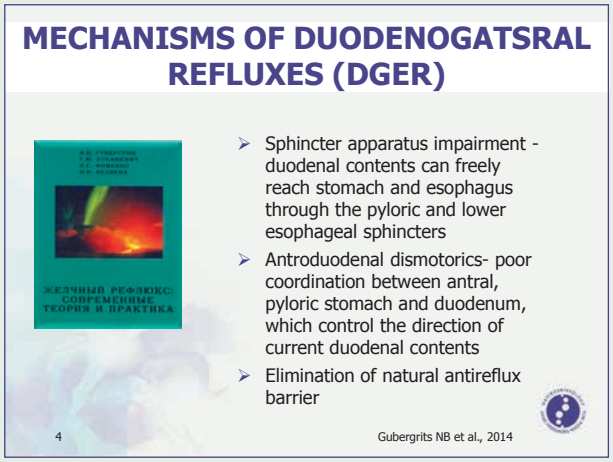
Results. Serious adverse events were not observed during the study, and the medications were well tolerated.

According to the preliminary data, during differentiated therapy the most patients noted clinical improvement – reduced heartburn, burping, bitter taste in the mouth, nausea, and pain syndrome. Endoscopic manifestations improved or did not change over time. According to the preliminary evaluation of the impedance-pH monitoring results, the total number of GER, the total percent reflux time, and the number of proximal refluxes reduced. These changes were noted not only in the groups receiving PPI therapy, but also in the group of patients receiving monotherapy by UDCA and combination therapy with the prokinetic agent.

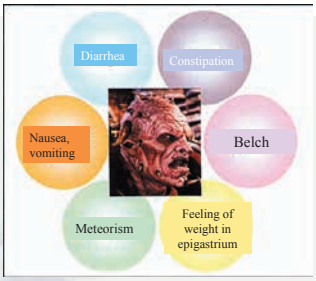
Conclusion. The results of the study show that the differentiated approach to therapy of patients with non-acid GERs contributes to higher efficacy of the treatment; PPIs for these patients may be considered only as concomitant medications for the treatment of GERD. Further analysis will be carried out in the revealed group of patients with mixed GERD (presence of acid and non-acid refluxes within 24 hours according to the impedance-pH monitoring results) because follow-up algorithms for these patients are currently not developed.

Simanenkov V.I. Questions of diagnostics and treatment of different forms of GERD. In: *11th International Symposium of Gastroenterology, Saint Petersburg, Russia, 12–14 May 2016*. [online].
Available from URL: http://www.promedcs.eu/sites/default/files/abstractbook_2016.pdf





DUODENAL DEMON SYNDROME



Butorova LI Syndrome of duodenal hypertension; clinical significance and treatment / LI Butorova// Duodenum in health and impaired state: current issue and clinical perspectives: (XI Ros. Gastroenterol. Week). - M .:, 2005.-P. 17-30.Буторова Л. И. Синдром дуоденальной гипертензии, клиническое значение и лечение/

5

REFLUXATE AT DGER

- Total concentration of bile acids in esophagus with erosive esophagitis is 124 mmol/l, and in Barrett's esophagus and/or stricture - above 200 mmol/l, whereas in the control - 14 mmol/l.
- In patients with GERD and Barrett's esophagus 80% of cases id associated with mixed refluxate, and erosive esophagitis showed such refluxate only in 40% of cases.
- Bile acid pool was represented mainly by cholic, glycocholic and taurocholic acids.

Nehra D. Composition of the refluxate / D. Nehra // Barrett's esophagus. – Paris : John Libbey Eurotext, 2003. - Vol. 1. - P. 18 - 22.

6

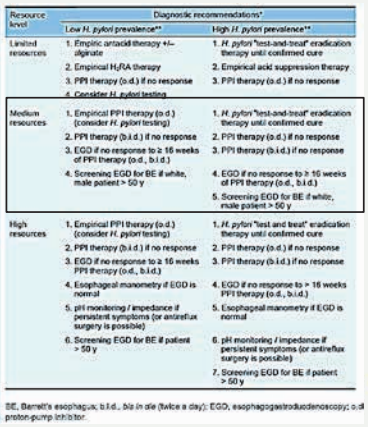
CLINICAL FEATURES OF DGER

- M.F. Vaezi and J.E. Richter pointed out that in contrast to the "classical" acid reflux manifested by heartburn, regurgitation and dysphagia, DGER association with the appropriate symptoms is less pronounced
- More often than at acid reflux there are symptoms of dyspepsia
- Patients may complain of pain in the epigastric region, worsening after eating, sometimes reaching considerable intensity, nausea, vomiting with bile Apparently, this clinical picture should be supplemented by bitterness test in the mouth

Lapina TL, Bueverov SA Bitterness test in the mouth: the interpretation by gastroenterologist // Clinical prospects of gastroenterology, hepatology. 2013. №3.
Vaezi M.F., Richter J.E. Double reflux: double trouble // Gut. - 1999. - Vol. 44 -P. 590-592.

7

GERD – DIAGNOSTIC CASCADE



WGO, 2015

8

POSSIBILITIES OF ESOPHAGEAL PH-IMPEDANCE

- Detection of all types refluxes irrespective of refluxate pH (acidic, alkaline, slight acidic reflux and extrareflux)
- Diagnosis of GERD during therapy with antisecretory drugs and evaluation of its effectiveness, as well as at hypo/anatsidnyh states
- Identification of links between existing symptoms and slightly acidic, weakly alkaline refluxes
- Determination of physical condition refluxate (gas, liquid, and mixed)
- Determination of height of proximal reflux distribution
- Calculation of bolus clearance

9

Trukhmanov A.S. et al., 2013

24h multichannel pH impedance

ZepHr register

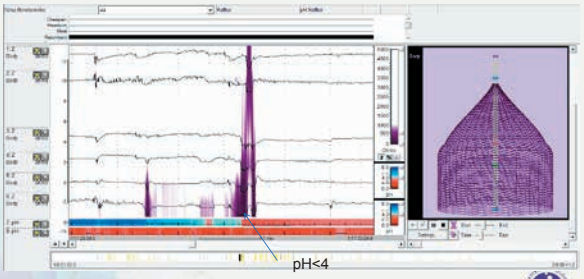
Probes

Calibration kit

Lower esophageal sphincter locator

10

Acid GER



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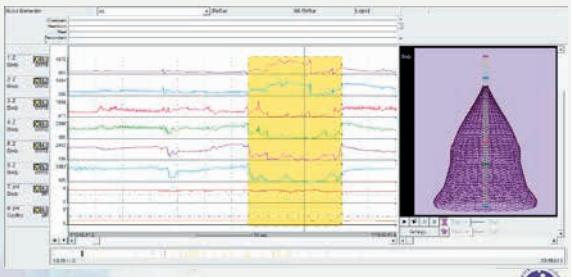
Slight acid GER



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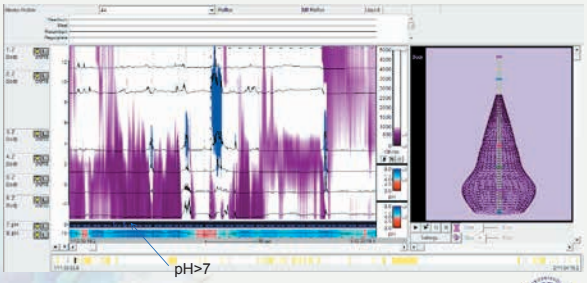
Alkaline reflux



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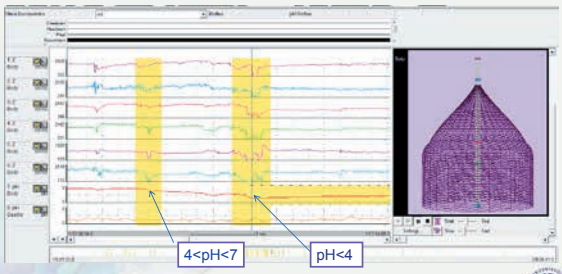
Mixed GER



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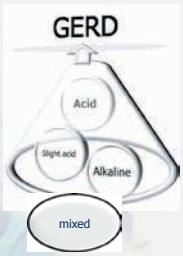
GETEROGENICITY OF GERD

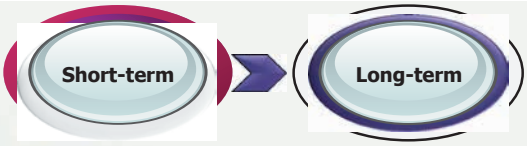


- Refluxate has predominantly acidic character in 50% of patients with GERD,
- The acidic character of a component of bile occurs in 39.7% of cases
- 10.3% of patients have bile reflux.
- Associated reflux

15

Talley N. et al., 2006 Truhmanov AS et al., 2014 Simanenkov VI et al., 2015

GERD TREATMENT GOALS



Initial therapy:
- Rapid relief of symptoms
- Esophagitis healing

Supporting therapy:
- Relapse prevention

Complications, including stricture, Barrett's esophagus, adenocarcinoma

16

Koya DL, Castell DO. Pract Gastroenterol 2006 – Vol.29, №1. Cutler A et al. Dig Dis Sci. 2010;55(2):338-45
Freston JW, Triadafilopoulos G. Aliment Pharmacol Ther. 2004;19 Suppl 1:35-42.

TREATMENT CASCADE 1. RESTRICTED RECOURSES

- Lifestyle modifications (diet, weight loss) to minimize symptoms
- Locally available symptomatic remedies if they are safe, effective, and less costly than prescription medications
- Most effective available acid-suppression therapy
- Step-up therapy — AA, H_2RA, PPI o.d., PPI b.i.d. — as available
- Stop therapy after 8 weeks to assess response
- Resume therapy, as needed, at lowest effective dose
  - — Intermittent
  - — On demand
- Continuous therapy for patients with (a) frequent symptoms, (b) stricture, (c) BE (to control symptoms)
- Consider *H. pylori* "test-and-treat" for patients on continuous PPI therapy

17

WGO,2015

TREATMENT CASCADE 2. AVERAGE RECOURSES

- PPI o.d. for 8–12 weeks, then reassess
- PPI b.i.d. for 8–12 weeks for persistent symptoms
- Switch PPIs to a modified-release PPI (effect lasting > 14 h/day, MR-PPI) if available (o.d. or b.i.d.)
- Stop therapy on symptom resolution to assess response
- Resume therapy, as needed, at lowest effective dose
  - — Intermittent
  - — On demand
- Lifestyle modifications (diet, weight loss) to minimize symptoms
- Continuous therapy for patients with (a) frequent symptoms, (b) stricture, (c) BE (to control symptoms)
- Consider *H. pylori* "test-and-treat" for patients on continuous PPI therapy
- Laparoscopic antireflux surgery for structural disease (hiatus hernia) or volume reflux causing regurgitation, aspiration, stricture, or persistent nocturnal symptoms despite PPI b.i.d.

18

WGO,2015

TREATMENT CASCADE 3. HIGH RECOURSES

High resources

- MR-PPI o.d. for 8–12 weeks, then reassess
- MR-PPI b.i.d. for 8–12 weeks for persistent symptoms
- More frequent PPI therapy if incomplete response symptomatically and on pH monitoring
- Stop therapy on symptom resolution to assess response
- Resume therapy, as needed, at lowest effective dose
  - — Intermittent
  - — On demand
- Lifestyle modifications (diet, weight loss) to minimize symptoms
- Continuous therapy for patients with (a) frequent symptoms, (b) stricture, (c) BE (to control symptoms)
- Consider *H. pylori* "test-and-treat" for patients on continuous PPI therapy
- Laparoscopic antireflux surgery for structural disease (hiatus hernia) or volume reflux causing regurgitation, aspiration, stricture, or persistent nocturnal symptoms despite PPI b.i.d.

AA, alginate–antacid; BE, Barrett's esophagus; b.i.d., *bis in die* (twice a day); H_2RA, histamine H_2 *omni die* (daily); MR-PPI, modified-release proton- pump inhibitor; PPI, proton-pump inhibitor.

19

WGO,2015

RGA GUIDELINES ON DRER TREATMENT

- For DGER various combinations (including those with PPI) of the following drugs could be admistered: adsorbents, antacids, prokinetics, ursodeoxycholic acid, alginic acid.
- In case of biliary reflux adsorbents and destination administration goal is not only includes neutralizing hydrochloric acid, but adsorption of bile acids and lysolecithin, and increase of mucosal resistance to damaging effects of aggressive factors.
- The basis for the use of ursodeoxycholic acid is its cytoprotective effect.

20

Ivashkin V.T. et al., 2014

PROKINETICS IN RGA GUIDELINES

- Lead to restoration of normal physiological condition of esophagus, acting effectively on the pathogenetic mechanisms of GERD, reduce the number of transient lower esophageal sphincter relaxations, improve esophageal clearance including improving of motor function of digestive tract lower divisions.
- Prokinetic Itopride hydrochloride refers pathogenetic treatment drugs of GERD, because it normalizes motor function of the upper gastrointestinal tract.

21

Ivashkin V.T. et al., 2014

EFFECT OF UDCA ON DGER

- Increase of concentration of UDCA in refluxate reduces its damaging properties due to replacement of hydrophobic bile acid pool and prevention of induced apoptosis of epithelial cells
- Anti-inflammatory and immunomodulating effects of UDCA may reduce the severity of symptoms
- Reduced risk of malignancy in Barrett's esophagus
- Prokinetic effect of UDCA on duodenal zone

22

Kurtz W. Therapeutische Wirkungen der Ursodeoxycholsaure (UDC) an Leber und Magen-Darm-Trakt / W. Kurtz // Verdauungskrankheiten. - 1992.-Vol. 10.-P. 153- 162.

DGER AND PPI

- Inadequate antisecretory therapy may increase the proportion of slightly acid reflux among the total number of reflux episodes.
- Use of pH-impedance in patients with refractory to a daily dose of PPIs showed changing of nature of reflux prior to and during therapy.
- If, before PPI receiving there was mostly acid reflux, during therapy - mostly slight acidic, and the number of reflux has not changed.
- **PPIs, providing suppressive effect on the proton pump transform acidic reflux to non-acid**
  More than 90% of reflux episodes emerging during therapy by PPIs are slight acidic
  Thus slight acidic reflux causes the same complaints (heartburn, regurgitation), as well as acidic reflux

Vela M. F. , et al., Simultaneous intraesophageal impedance and pH measurement of acid and nonacid gastroesophageal reflux: effect of omeprazole //Gastroenterology. - 2001. - Vol. 120. - P. 1599 - 1606.

23

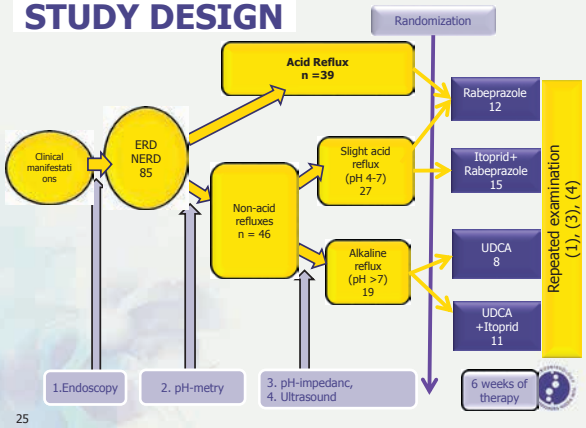
«The possibility of optimizing the diagnosis and therapy of different variants of gastroesophageal reflux disease» - «STOPHERD»

Study type: open, controlled, prospective monocentral, randomized, comparison

24

Simanenkov V.I., Lischuk N.B. 2014

STUDY DESIGN



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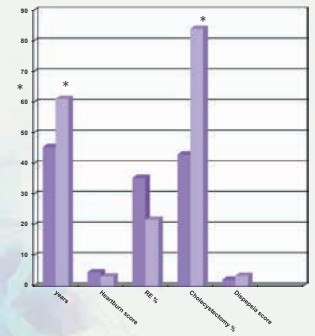
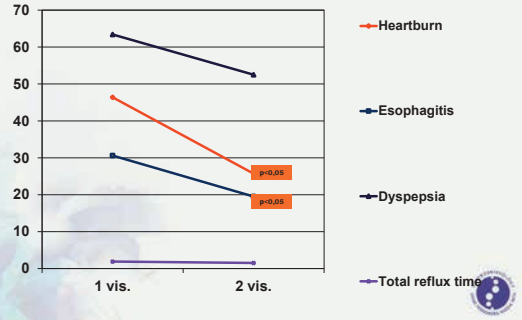
CLINICAL FEATURES OF SLIGHT ACID AND SLIGHT ALKALINE GER



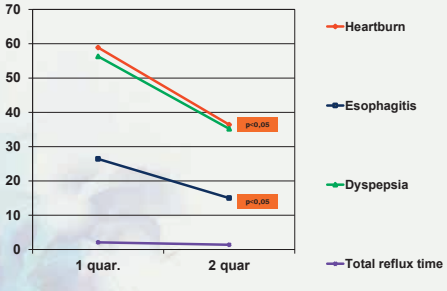
26

DYNAMICS OF CLINICAL MANIFESTATIONS IN PATIENTS WITH SLIGHTLY ACIDIC REFLUXES AGAINST PPI THERAPY



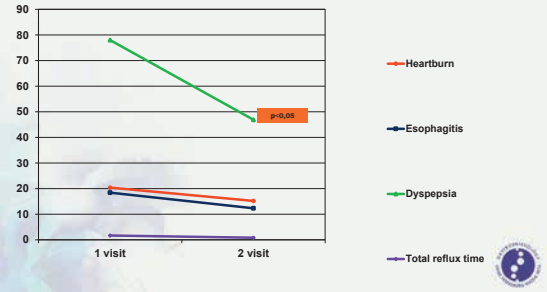
27

DYNAMICS OF CLINICAL MANIFESTATIONS IN PATIENTS WITH SLIGHTLY ACIDIC REFLUXES AGAINST PPI+ITOMED THERAPY



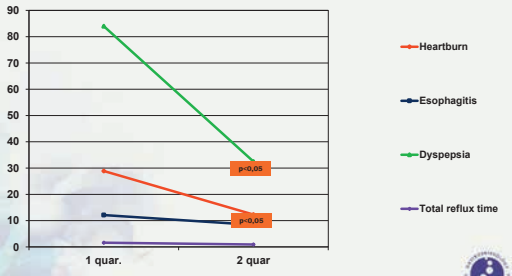
28

DYNAMICS OF CLINICAL MANIFESTATIONS IN PATIENTS WITH SLIGHT ALKALINE REFLUXES AGAINST UDCA THERAPY



29

DYNAMICS OF CLINICAL MANIFESTATIONS IN PATIENTS WITH SLIGHT ALKALINE REFLUXES AGAINST UDCA+ITOMED THERAPY



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CONCLUSION

- Patients with slight acidic reflux (27) had the following significant differences from patients with slight alkaline refluxes: heartburn that occurs on a daily basis and affects lifestyle (severe) was observed in the group with the "slight acid" GER in 46.4% and only in 18.2 % patients with " slight alkaline" GER ($p < 0.05$), for this group dyspepsia symptoms were less common, with less common history of cholecystectomy (43% and 84%)
- Against monotherapy with PPIs in patients with slightly acidic refluxes heartburn and the percentage of reflux esophagitis significantly decreased (30.6% -19.5%).
- Against concomitant PPI + Itomed treatment in patients with slightly acidic refluxes heartburn significantly reduced and total percentage of reflux time decreased from 2.1 to 1.4.

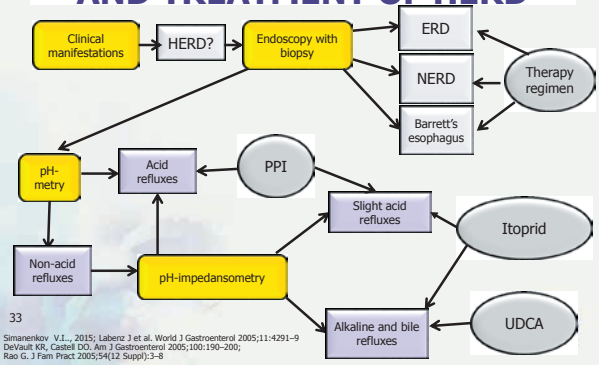
31

CONCLUSION

- Against monotherapy with UDCA of "slightly alkaline" GER the percentage of patients with dyspepsia significantly decreased , but endoscopic and significant differences in pH impedansometric were not identified (probably – against small patient sample).
- Against combination therapy with UDCA and itomed total number of gastroesophageal refluxes (from 62.5 to 45.4) and the number of "non-acidic" GER (from 33.5 to 15.6) significant decreased.

32

ALGORITHM OF DIAGNOSTICS AND TREATMENT OF HERD



33

Simanenkov V.I., 2015; Labenz J et al. World J Gastroenterol 2005;11:4291–9
DeVault KR, Castell DO. Am J Gastroenterol 2005;100:190–200;
Rao G. J Fam Pract 2005;54(12 Suppl):3–8

Thank you for your attention

Progress is outside the standard perception of the world

A. Einstein

34

UPDATE IN MANAGEMENT OF GASTROESOPHAGEAL REFLUX DISEASE (GERD)

Peter MALFERTHEINER

University of Magdeburg, Department of Gastroenterology, Hepatology and Infectious Diseases, Magdeburg; Germany

Gastroesophageal reflux disease (GERD) is among the top listed diseases leading to a high frequency of medical consultations in outpatient settings (1). The clinical spectrum of GERD embraces esophageal symptoms (heartburn, regurgitation) in the presence but as well in the absence of esophageal lesions (NERD/ERD). GERD presdisposes to preneoplastic lesions (Barrett's esophagus) and to a variety of extraesophageal symptoms. It is more than 25 years, since PPI have been introduced in the clinical practice and they represent the mainstay in GERD therapy. However, more recently PPI have been recognized for their therapeutic limitations in a variety of GERD related conditions (2).

PPI inadequate responsiveness of GERD-related symptoms is a big problem. The challenge is the correct diagnosis of GERD in patients presenting with normal esophageal mucosa by conventional white light endoscopy (non erosive GERD = NERD). The allocation of these patients to

a) "true" NERD,

b) acid hypersensitive esophagus,

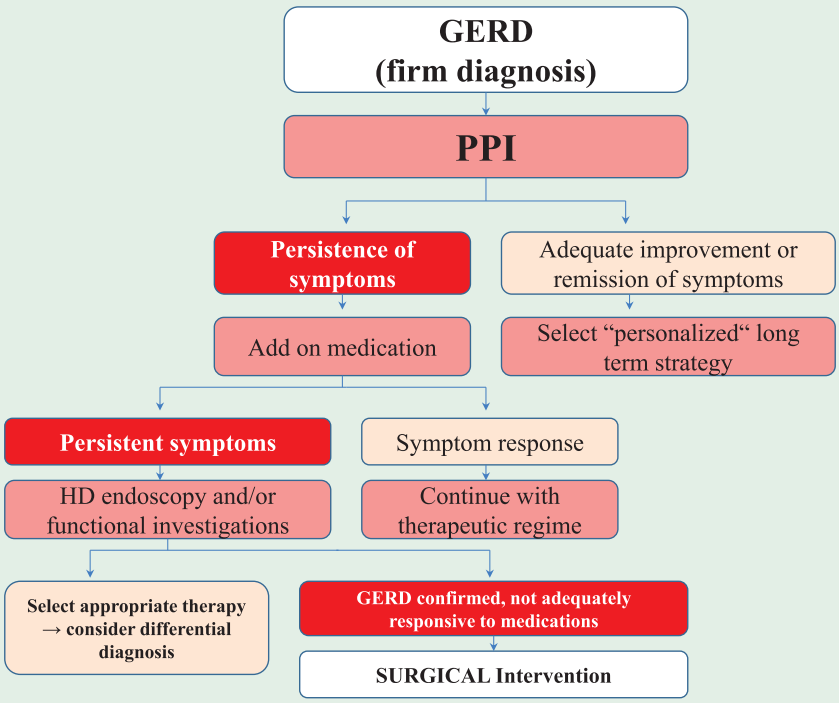
c) non acid hypersensitive esophagus and

d) functional heartburn is crucial.

New HD endoscopy and functional methods contribute to make a firm diagnosis.

Only with an accurate diagnosis of these conditions, targeted treatment strategies have a high probability of success (3).

For optimizing the therapy in GERD proper timing and dosing of PPI are essential. In case of PPI non – or partial responsiveness "add on" therapies are required and they include medications acting either on the mucosal resistance or by interfering with other reflux mechanisms (4–7). Several functional gastrointestinal disorders are overlapping with GERD and may require the addition of medications targeting dyspepsia and symptoms related to the irritable bowel syndrome (IBS). While the large majority of patients with GERD are best manageable with medications, selected cases may benefit from surgery (i.e. laparoscopic fundoplication). Recently several implantable devices have been developed and successfully tested for improvement of the antireflux barrier. At present, they need to be critically viewed and wisely chosen for the management of the appropriate patient. Modern management of GERD is guided by high level evidence based studies, but for individual patient treatment we need to respect criteria of personalized medicine. A proposed algorithm for management is in tab. 1.



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2) Boeckxstaens G., El-Serag H.B., Smout A.J., Kahrilas P.J. Symptomatic reflux disease: the present, the past and the future. Gut 2014; 63(7): 1185–1193.

3) Sigterman K.E., van Pinxteren B., Bonis P.A., *et al*. Short-term treatment with PPI, H_2-receptor antagonists and prokinetics for gastro-oesophageal reflux disease like symptoms and endoscopy negative reflux disease. Cochrane Database Syst Rev 2013; 5: CD002095.

4) Kahrilas P.J., McColl K., Fox M., *et al*. The acid pocket: a target for treatment in reflux disease? Am J Gastroenterol 2013; 108: 1058–1064.

5) Woodland P., Sifrim D. Oesophageal mucosal barrier: a key factor in the pathophysiology of non-erosive reflux disease (NERD) and a potential target for treatment. Gut 2014; 63: 705–706.

6) Savarino E., Zentilin P., Savarino V. NERD: an umbrella term including heterogeneous subpopulations. Nature Rev Gastroenterol Hepatol 2013; 10: 371–380.

7) Kandulski A., Malfertheiner P. Gastroesophageal reflux disease – from reflux episodes to mucosal inflammation. Nat Rev Gastroenterol Hepatol 2011; 9(1): 15–22.

Malfertheiner P. Update in management of gastroesophageal reflux disease (GERD). In: *11th International Symposium of Gastroenterology, Saint Petersburg, Russia, 12–14 May 2016*. [online].
Available from URL: http://www.promedcs.eu/sites/default/files/abstractbook_2016.pdf

11th International Symposium of GASTROENTEROLOGY
12–14 May 2016, Saint Petersburg, Russia

HOW TO OPTIMIZE MEDICAL THERAPY IN GERD

Peter Malfertheiner

Klinik für Gastroenterologie, Hepatologie und Infektiologie
Otto-von-Guericke Universität Magdeburg
GERMANY

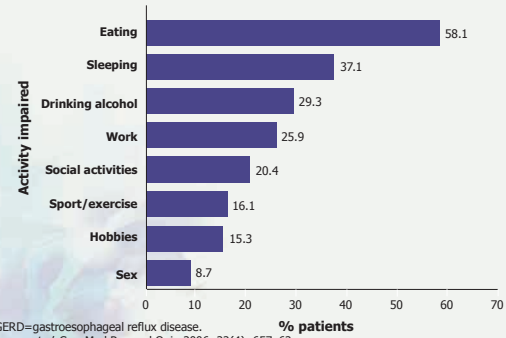
GERD
has an epidemic character

Leading Diagnoses in the Ambulatory Setting for Gastrointestinal, Liver and Pancreatic Disorders in the United States, 2010

Rank	Diagnosis	Estimated no. of visits: Office visits	ED	Hospital outpatient department	Total	ICD-9-CM codes
1	Abdominal pain	9,232,817	6,476,136	970,318	16,678,271	789.00
2	Gastroesophageal reflux and reflux esophagitis	6,222,275	294,942	549,992	7,067,209	530.11, 530.81
3	Hemorrhoids	3,592,945	126,128	226,505	3,930,576	455
4	Constipation	2,905,705	530,827	280,129	3,716,661	564.0
5	Nausea and vomiting	1,404,566	1,969,949	215,701	3,590,214	787.0
6	Abdominal wall and inguinal hernia	2,852,677	204,375	422,937	3,479,989	550, 553.0, 553.1, 553.2, 553.9
7	Malignant neoplasm of the colon or rectum	2,420,460	2,420	386,783	2,809,666	153, 154
8	Diverticular disease	2,275,436	262,910	195,771	2,734,119	562.1
9	Diarrhea	1,943,572	533,181	197,071	2,673,824	787.91
10	Gastritis and dyspepsia	1,902,990	472,165	234,836	2,609,994	535, 536.8
11	Irritable bowel syndrome	2,290,466	24,121	89,170	2,403,761	564.1
12	Crohn's disease	1,722,664	44,641	121,256	1,888,561	555
13	Cholelithiasis	872,040	355,504	119,166	1,346,710	574
14	Dysphagia	1,021,034	38,264	113,664	1,172,962	787.2
15	Rectal bleeding	648,827	176,160	61,772	886,759	569.3
16	Benign neoplasm of colon and rectum	726,675		144,775	871,450	211.3, 211.4
17	Pancreatitis	409,862	326,418	91,492	827,772	577, 577.1
18	Ulcerative colitis	633,446	17,166	72,763	723,374	556
19	Hepatitis C infection	563,442	19,496	90,334	673,272	070.41, 070.44, 070.51, 070.54, 070.7
20	Appendicitis	317,374	195,150	128,524	641,048	540, 541, 542
21	Hepatitis, unspecified	554,749	3212	9573	567,534	573.3
22	Chronic liver disease and cirrhosis	438,914	30,084	78,957	547,955	571
23	Barrett's esophagus	368,738		47,883	416,622	530.85
24	Celiac disease	23,521		4472	27,993	579.0

Peery, *et al.* Gastroenterology 2015 Dec; 149(7): 1731–1741

IMPACT OF GERD ON DAILY ACTIVITIES



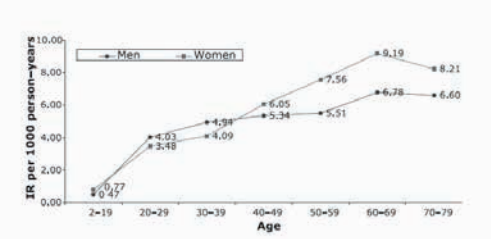
GERD=gastroesophageal reflux disease.
Jones, *et al.* Curr Med Res and Opin 2006; 22(4): 657–62

GERD

- Increases with age
- High prevalence in pregnant women
- High impact of obesity

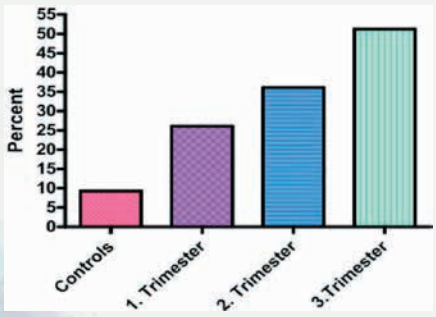
GERD AND AGE

Incidence rate of *GERD diagnosis* (ICD8-5300) in 7,151 patients from UK general practices



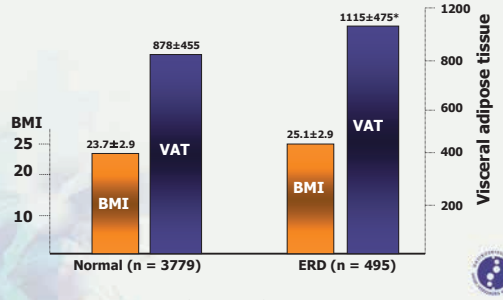
Ruigomez, *et al.* APT 2004; 20: 751

PREVALENCE OF GERD IN PREGNANCY COMPARED TO NON-PREGNANT CONTROL GROUP



Fill Malfertheiner S., *et al.* BMC Gastroenterol. 2012 Sep 24; 12: 131

BMI VS VAT IN EROSIVE ESOPHAGITIS



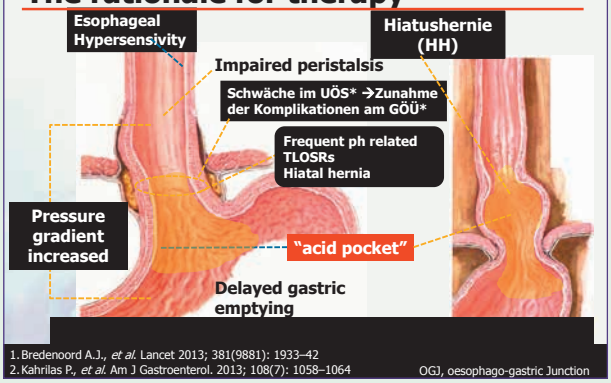
Nam, *et al.* Gastroenterology 2010; 139: 1902–1911

GERD and obesity

Not BMI or waist circumference but abdominal visceral adipose tissue volume is associated with increased risk of GERD in males ∞ females

Nam, *et al.* Gastroenterology 2010; 139: 1902–1911

GERD – Pathophysiology
The rationale for therapy



1. Bredenoord A.J., *et al.* Lancet 2013; 381(9881): 1933–42
2. Kahrilas P., *et al.* Am J Gastroenterol. 2013; 108(7): 1058–1064

OGJ, oesophago-gastric Junction

GERD MANAGEMENT

Life style modifications and weight reduction First step in therapeutic management

THE CHANGING LIFESTYLE OF TODAY'S PATIENT

- A change in work-life balance over the years has impacted meal times[1]
- Europeans skip breakfast 20% of the time and approximately 20% have breakfast once a week or less[1,2]
- Increased stress due to a hectic work-life may lead to a decrease in medication adherence[3]

1. European Foundation for the Improvement of Living and Working Conditions Establishment Survey on Working Time 2004–5; www.eurofound.eu.int; http://www.eu-patient.eu/Documents/Policy/Adherence-compliance-concordance/Adherence%20-%20Joint%20briefing%20paper.pdf
2. Medi-Voice project http://cordis.europa.eu/fetch?CALLER=FP6_PROJ&ACTION=D&DOC=3019&CAT=PROJ&QUERY=1170700793308&RCN=75025
3. World Health Organisation. Adherence to long-term therapies. 2003. http://www.who.int/chp/knowledge/publications/adherence_full_report.pdf. Accessed 7 February 2014

WHICH NUTRIENTS ARE CONSIDERED HARMFUL IN GERD?

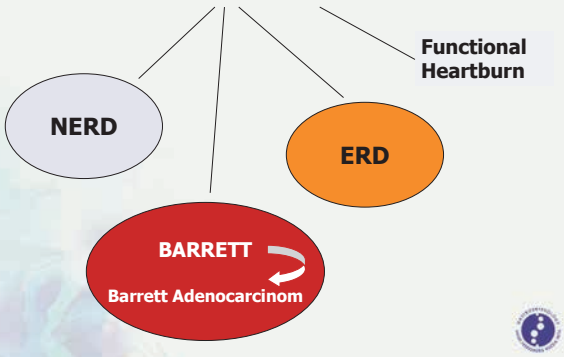
Factor	Trials No.	Worsened pH	Worsened Symptoms	References
Tobacco	**12**	**B**	**B**	**6-17**
Alcohol	**16**	**B**	**B**	**3,6,9,10,16,-27**
Coffee and caffeine	**14**	**E**	**No effect (C)**	**10,1,17,52-62**
Chocolate	2	B	E	63,64
Spicy foods	2	E	C	3,65
Citrus	3	E	C	52,66,67
Carbonated beverages	2	E	C	68,69
Fatty foods	9	B	E	70-78
Mint	1	E	E	79

Grade of evidence A-E

Kaltenbach, *et al.* Arch Intern Med 2006; 166: 965–971

Chattopadhyay DK, Greaney MG, Irvin TT. Effect of cigarette smoking on the lower oesophageal sphincter. *Gut.* 1977;18:833-835
Kahrilas PJ, Gupta RR. Mechanisms of acid reflux associated with cigarette smoking. *Gut.* 1990; 31:4-10.
Schindlbeck NE, Heinrich C, Dendorfer A, Pace F, Muller-Lissner SA. Influence of smoking and esophageal intubation on esophageal pH-metry. *Gastroenterology.* 1987;92:1994-1997.
Bujanda L. The effects of alcohol consumption upon the gastrointestinal tract.*Am.JGastroenterol.* 2000;95:3374-3382.
Vitale GC, Cheadle WG, Patel B, Sadek SA, Michel ME, Cuschieri A. The effect of alcohol on nocturnal gastroesophageal reflux. *JAMA.* 1987;258:2077-2079.
Grande L, Monforte R, Ros E, et al. High amplitude contractions in the middle third of the oesophagus: a manometric marker of chronic alcoholism? *Gut.* 1996;38:655-662
Price SF, Smithson KW, Castell DO. Food sensitivity in reflux esophagitis. *Gastroenterology.*1978;75:240-243.
Cohen S, Booth GH Jr. Gastric acid secretion and lower-esophageal-sphincter pressure in response to coffee and caffeine. *N Engl J Med.*1975;293:897-899.
Cohen S. Pathogenesis of coffee-induced gastrointestinal symptoms. *N Engl J Med.* 1980; 303:122-124.
Wendl B, Pfeiffer A, Pehl C, Schmidt [illegible] H. Effect of decaffeination of coffee on gastro-oesophageal reflux. *Aliment Pharmacol Ther.* 1994;8:283-287.

GERD SPECTRUM



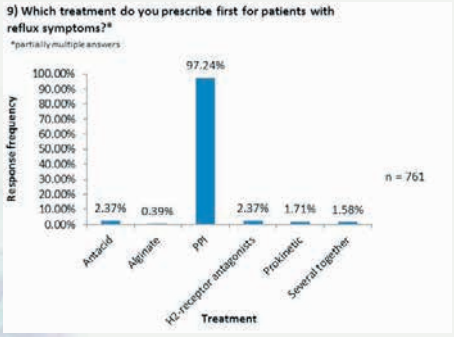
GERD

Broad spectrum of clinical complications
- typical symptoms
- atypical symptoms

HEARTBURN

How do you treat?

SYMPTOMATIC GERD: PPI FIRST



Malfertheiner, *et al.* DDW 2015, MMW 2015

GERD THERAPY

PPI first choice

and safe

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

USE OF PROTON-PUMP INHIBITORS IN EARLY PREGNANCY AND THE RISK OF BIRTH DEFECTS

Björn Pasternak, M.D., PH.D., and Anders Hviid, Dr.Med.Sci. (2010)

Exposure to PPIs during the first trimester of pregnancy was

not associated with a significantly increased risk of major birth defects.

Pasternak, *et al.* N Engl J Med 2010; 363: 2114–23

GERD MANAGEMENT

- Typical Reflux symptoms [RS] an… …py
- Typical RS with normal co… …ndoscopy [NERD]
- Reflux esoph… …n endoscopy [ERD: LA A-B-C-D]
- C… …ations
  - …ricture
  - bleeding
- Barrett Esophagus

PPI for any degree of severity

HEARTBURN

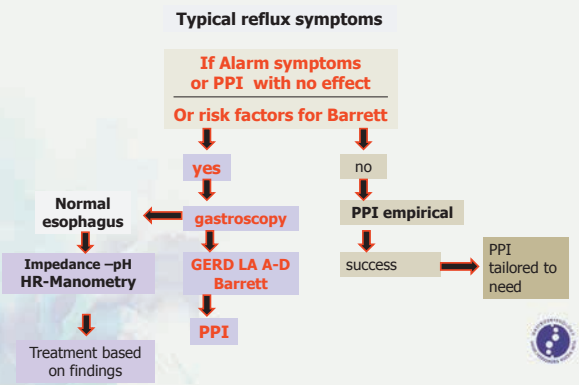
How do you treat?

Empirical

vs

full diagnostic assessment

GERD MANAGEMENT



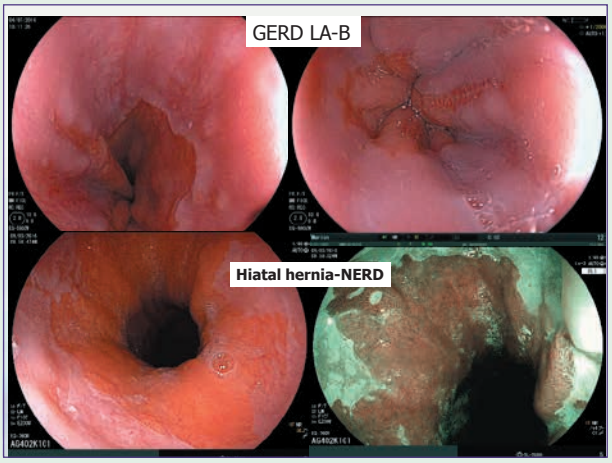
TYPICAL REFLUX SYMPTOMS

Endoscopic assessment

- erosive esophagitis (ERD)

- non erosive esophagitis (NERD)

- Barrett`s esophagus

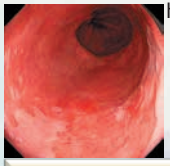


BARRETT - ESOPHAGUS

Thrift Clin Gastroenterol Hepatol. 2015 Dec; 13(13): 2225–32

Key facts:

- Premalignant condition for adenocarcinoma
  → risk 30–40increased
- 10% of patients with frequent reflux symptoms
  however also in 1–2% of the general population



95% of patients with BE have no progression to ca
→ only 5% of patients with adenoca have a known BE before the cancer diagnosis

Length of Barrett's oesophagus and cancer risk: implications from a large sample of patients with early oesophageal adenocarcinoma

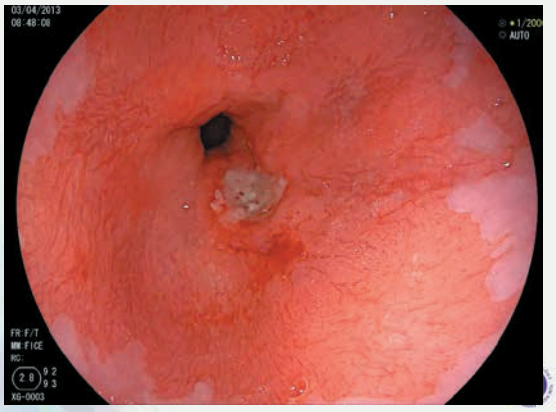
Heiko Pohl,[1,2] Oliver Pech,[3] Haris Arash,[4] Manfred Stolte,[5] Hendrik Manner,[4] Andrea May,[4,6] Klaus Kraywinkel,[7] Amnon Sonnenberg,[8] Christian Ell[4,6]

1071 T_1 EAC

	Annual cancer transition
56% long segment →	0.22%
24% short segment →	0.03%
20% ultrashort segment →	0.01%

To detect one cancer
→450 patients with long segment Barrett annual endoscopy

Gut. 2016 Feb; 65(2): 196–201



Barrett-Esophagus → EAC

Prevention

- Aspirin
- NSAIDs

→ 32% risk reduction

Statins	48% risk reduction
PPI	67% risk reduction
Metformin	? (1 negative study, Chan et al. 2015)

! Weight reduction !

Thrift et al. Clin Gastroenterol Hepatol. 2015 Dec;13(13):2225-32

BARRETT ESOPHAGUS TAKE HOME

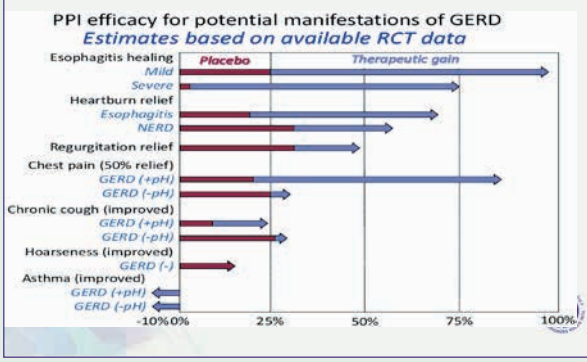
- no general screening recommended
- surveillance for selected groups only
- PPI long term
- statines on individual consideration
- aspirin, coxibs still candidates awaiting RCT
- RFA in low grade dysplasia should be considered

GERD THERAPY

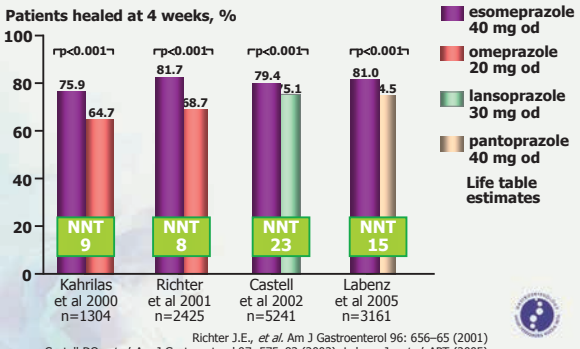
PPI first choice in all GERD – manifestations

SUMMARY OF PROTON PUMP INHIBITOR (PPI) EFFICACY FOR VARIOUS GERD SYNDROMES AS ASSESSED IN RANDOMIZED CONTROLLED TRIALS

Boeckxstaens, *et al.* Gut. 2014



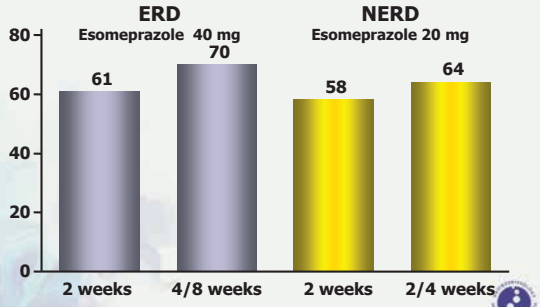
HEALING OF REFLUX ESOPHAGITIS ON PPIS



Richter J.E., *et al.* Am J Gastroenterol 96: 656–65 (2001)
Castell DO, *et al.* Am J Gastroenterol 97: 575–83 (2002); Labenz J., *et al.* APT (2005)

COMPLETE HEARTBURN RELIEF*

PROGERD STUDY
(n=6215)



*) = No heartburn according to RDQ

Malfertheiner, *et al.* GUT 2005

PPI therapy is equally effective in well-defined non-erosive reflux disease and in reflux esophagitis: a meta-analysis

MEDLINE (1966–2010), Cochrane Comprehensive Trial Register (1997–2010) and EMBASE (1985–2010) databases

	ERD	NERD
PPI 4 weeks complete relief	**0.72 (95% CI 0.69–0.74)** (eigth studies)	Endoscopy negative pH positive **0.73 (0.69–0.77)** (two studies)

Weijenborg, *et al.* Neurogastroenterol Motil 2012; 24: 747–e350

Systematic review: persistent reflux symptoms on proton pump inhibitor therapy in primary care and community studies

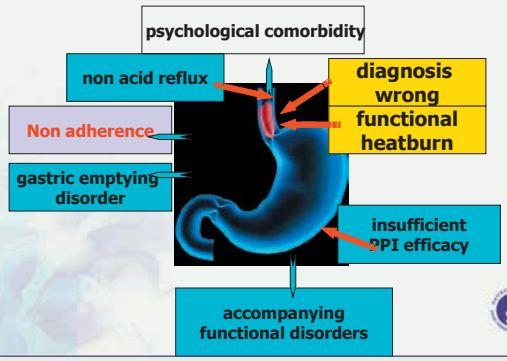
H. El-Serag*, A. Becher* & R. Jones†

Aliment Pharmacol Ther. 2010 Sep; 32(6): 720–37

- Nineteen studies in individuals with GERD taking a PPI included
- **randomized trials: 32% (25–39%) and 28% (26–30%), respectively.**
- observational primary care and community-based studies: **45% (30–60%) of participants reported persistent GERD symptoms**
- less likely in studies from Europe than in those from the USA (RR: 0.71; p < 0.001)

randomized trials

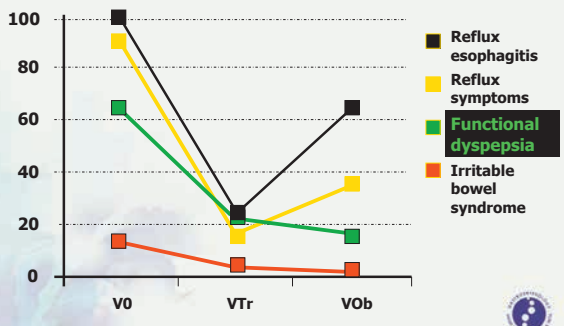
PPI NON RESPONSIVE GERD



PATIENT NOT SATISFIED?

Consider overlapping symptoms

RATES OF PATIENTS (%) WITH GASTROINTESTINAL DISORDERS ON PPI [INTENTION-TO-TREAT (ITT)].



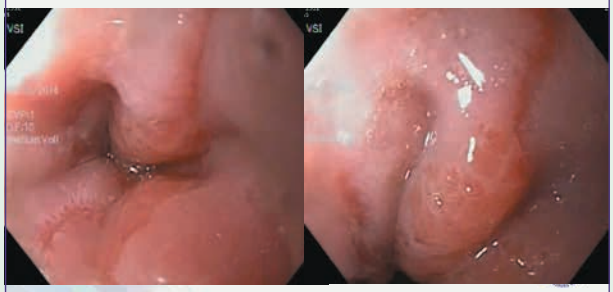
Mönnikes, *et al.* Aliment Pharmacol Ther 2012; 35: 1279–1289

HEARTBURN

Search for the cause!

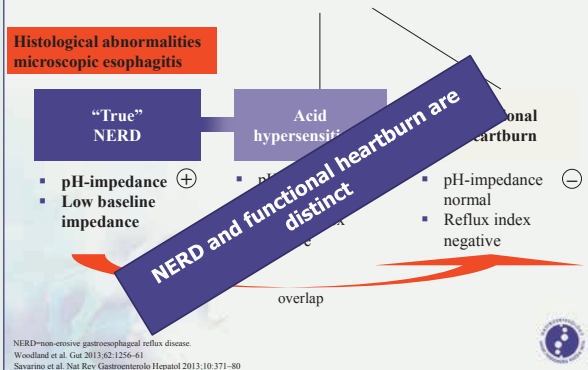
NERD OR „FUNCTIONAL HEARTBURN"?

pH-metry – pH-impedance – histology



NERD=non-erosive gastroesophageal reflux disease.

THE TRUE NERD PATIENT



NERD=non-erosive gastroesophageal reflux disease.
Woodland et al. Gut 2013;62:1256–61
Savarino et al. Nat Rev Gastroenterolo Hepatol 2013;10:371–80
Kandulski et al. Aliment Pharmacol Ther 2013;38:643–51

GASTROESOPHAGEAL REFLUX DISEASE

Correct diagnosis essential

- directs management
- saves costs

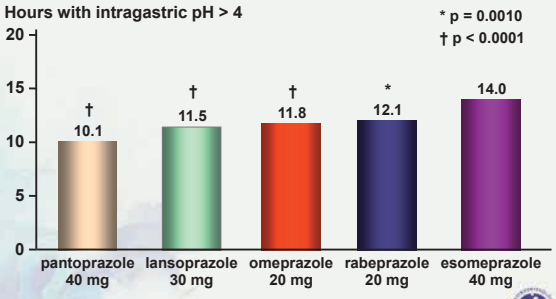
GERD

What to do if non responsive to PPI therapy in standard dose?

GERD

- Change the PPI?
- Increase the dose?
- Increase frequency of administration?
- Add on medication?

HOW DO INDIVIDUAL PPIS PERFORM? (5 WAY CROSSOVER STUDY)

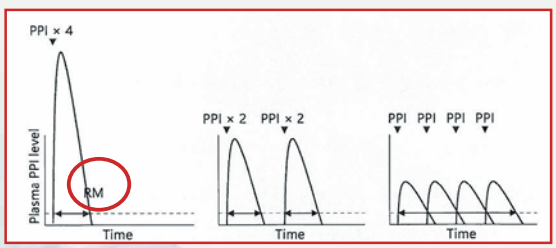


34 *H. pylori* negative GERD patients – Crossover Study

Miner P., *et al.* Am J Gastroenterol 2003; 98: 2616–20.

DOSING MATTERS

IN RAPID METABOLIZER (RM) PPI ADVISABLE 4 TIMES DAILY FOR SUFFICIENT PLASMA LEVELS OF PPI



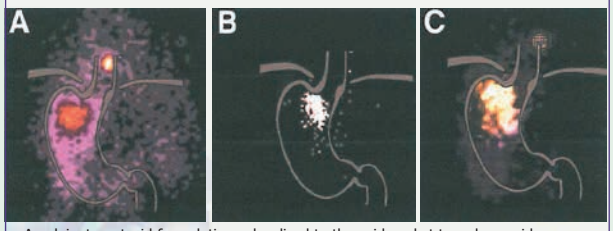
Furuta, *et al.* 2013
In Chiba Malfertheiner, Satoh (eds.)
Frontiers in Gastrointestinal research Karger

GERD: OPTIMIZING THERAPY

PPI – increase dose and frequency of administration
gaviscon dual
antacids
SSRI
reflux inhibitors?
prokinetics
H2-RA

SCINTIGRAPHIC IMAGES OF 99MTC-PERTECHNETATE-LABELED ACID POCKET, 111MIN-LABELED ALGINATE-ANTACID AND THE 2 SCINTIGRAPHIC RECORDINGS SUPERIMPOSED

Rohof, *et al.* Clinical Gastroenterology and Hepatology 2013; 11: 1585–1591



An alginate-antacid formulation colocalized to the acid pocket to reduce acid reflux in patients with gastroesophageal reflux disease

Randomised clinical trial: the clinical efficacy and safety of an alginate-antacid (Gaviscon Double Action) versus placebo, for decreasing upper gastrointestinal symptoms in symptomatic gastroesophageal reflux disease (GERD) in China

J. Sun*, C. Yang†, H. Zhao‡, P. Zheng§, J. Wilkinson¶, B. Ng¶ & Y. Yuan*

Randomised double-blind placebo-controlled parallel-group

Participants with symptomatic GERD (n = 1107) were randomised to receive Gaviscon DA or placebo (two tablets four times daily) for seven consecutive days.

Mean RDQ GERD scores: 2.51 for Gaviscon DA and 2.50 for placebo at baseline; 1.25 for Gaviscon DA and 1.46 for placebo post treatment.

Gaviscon DA tablets provide effective and safe reduction in acid reflux and dyspepsia symptoms in Chinese individuals with mild-to-moderate GERD

Sun, *et al.* Aliment Pharmacol Ther. 2015 Oct; 42(7): 845–54.

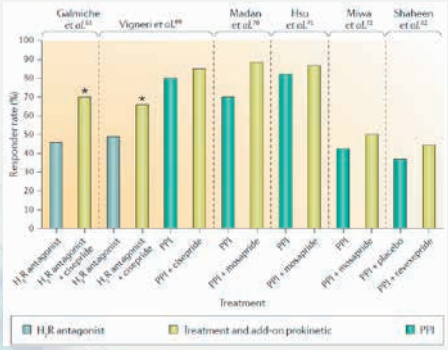
Addition of prokinetics to PPI therapy in gastroesophageal reflux disease: A meta-analysis

Li-Hua Ren, Wei-Xu Chen, Li-Juan Qian, Shuo Li, Min Gu, Rui-Hua Shi

- twelve RCTs including 2,403 patients
- combined therapy was associated with a greater symptom score change (95%CI: 2.14–3.02, P < 0.00001)

World J Gastroenterol. 2014 Mar 7; 20(9): 2412–9.

RESPONDER RATES IN STUDIES INVESTIGATING THE EFFECT OF PROKINETIC DRUGS AS ADD-ONS TO ACID-SUPPRESSIVE THERAPY FOR REFRACTORYGERD



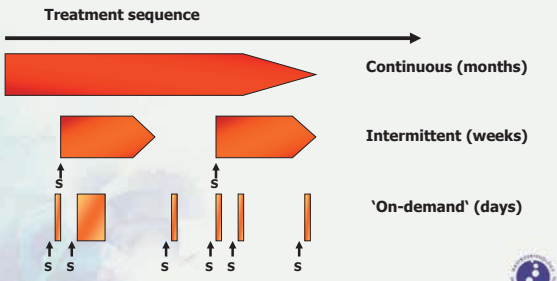
Scarpellini, *et al.* Nature Reviews epub2016.

GERD

Long term

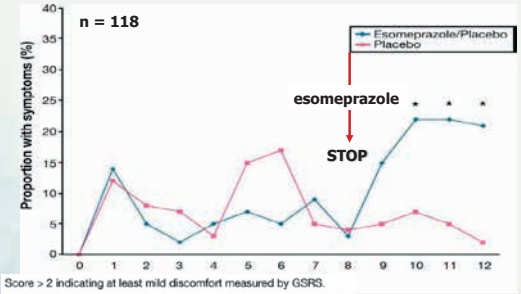
Personalized therapy

PERSONALIZED LONG-TERM STRATEGIES FOR THE TREATMENT OF GERD



S = systematic recurrent use

WATCH OUT! PPI ACID REBOUND (IN HEALTHY VOLUNTEERS)



Score > 2 indicating at least mild discomfort measured by GSRS.
The PPI/placebo group received esomeprazole 40 mg o.d in weeks 1-8 followed by placebo in weeks 9-12.
The placebo group received placebo tablets in week 1-12.
* : P< 05

Reimer et al. Gastroenterology. 2009 Jul; 137(1): 80–7, 87.

ORIGINAL CONTRIBUTION | CLINICIAN'S CORNER

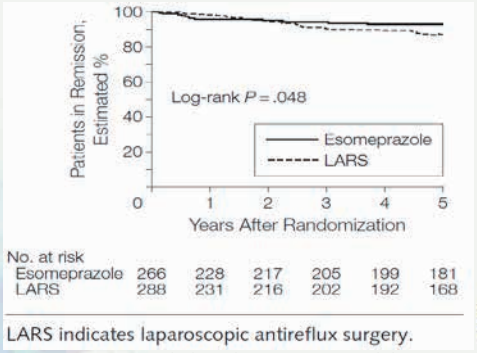
Laparoscopic Antireflux Surgery vs Esomeprazole Treatment for Chronic GERD

The LOTUS Randomized Clinical Trial

Jean-Paul Galmiche, et al

JAMA, May 18, 2011—Vol 305, No. 19

TIME TO TREATMENT FAILURE



LARS indicates laparoscopic antireflux surgery.

Galmiche, *et al.* JAMA, May 18, 2011; 305(19)

How safe are PPI? Never ending story

PPI risks in focus

What effects beyond acid suppression?

- **Gastrointestinal Functions and Structure**
- **Hypocalcemia, osteoporosis, bone fractures**
- Hypomagnesemia
- Vitamin B_{12} deficiency
- Iron deficiency
- **Gastrointestinal Infections**
  - **Gastric microbiota changes**
  - **Small bowel bacterial overgrowth**
  - ***Clostridium difficile and other enteric* infections**
  - **Spontaneous Bacterial Peritonitis**
  - **Other infections (pneumonia)**

Laboratory variables (median values) in patients treated with anti-reflux surgery (ARS) or a proton pump inhibitor

Attwood, *et al.* Aliment Pharmacol Ther. 2015 Jun; 41(11): 1162–74.

No abnormalities

Laboratory variable (treatment group)	N	SOPRAN Baseline	1 year	3 years	5 years	LOTUS N	Baseline	1 year	3 years	5 years
Vitamin B_{12} (pmol/L)										
ARS group	110–132	333	309	321				297	298	289
PPI group	123–143	330	328	332				320	320	317
Gastrin (pmol/L)										
ARS group	101–123	19	14				25	23	23	24
PPI group	117–131	18	38			9–265	24	54	55	62
Chromogranin A (ng/mL)										
ARS group	N/A	N/A				157–245	57.9	38.0	34.7	40.6
PPI group	N/A				N/A	180–265	57.6	123.4	147.4	145.8
Ferritin (µg/L)										
ARS group			55	80		158–245	111	109	120	122
PPI group			67	79		180–265	118	131	133	156
Homocysteine (µ										
ARS group		N/A	N/A	N/A		157–245	10.6	10.8	10.3	11.8
PPI group		N/A	N/A	N/A		180–265	10.7	11.1	10.7	11.7
Calcium (mmol/L)										
ARS group	102–134	2.4	2.3	2.4	2.3	151–243	2.3	2.3	2.3	2.3
PPI group	119–146	2.3	2.3	2.3	2.3	183–265	2.4	2.4	2.3	2.3
Vitamin D (nmol/L)										
ARS group	N/A	N/A	N/A	N/A	N/A	157–245	45	58	52	48
PPI group	N/A	N/A	N/A	N/A	N/A	180–265	46	59	56	49

Community-acquired respiratory tract infections in patients receiving esomeprazole: a retrospective analysis of patient-level data in placebo-controlled studies.

Estborn, *et al.* Aliment Pharmacol Ther. 2015 Sep; 42(5): 607–13.

- 24 randomised, double-blind clinical studies
- 9062 patients on ESO vs 5500 on placebo

- The relative risk for any respiratory tract infection in patients receiving esomeprazole compared with placebo was 0.94 (95% CI, 0.86–1.04).
- For lower respiratory tract infections, the relative risk was 0.82 (95% CI, 0.65–1.03) and for pneumonia, 0.66 (95% CI, 0.36–1.22).

No causal association between treatment with esomeprazole and the occurrence of community-acquired respiratory tract infections, including pneumonia.

Association of Proton Pump Inhibitors With Risk of Dementia
A Pharmacoepidemiological Claims Data Analysis

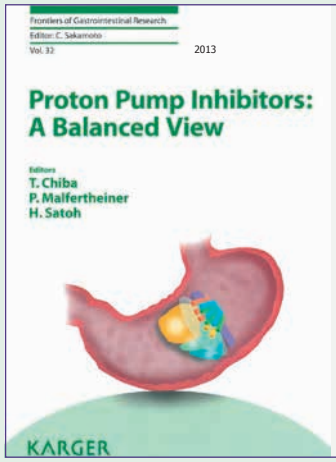
Willy Gomm, PhD; Klaus von Holt, MD, PhD; Friederike Thomé, MSc; Karl Broich, MD; Wolfgang Maier, MD; Anne Fink, MSc; Gabriele Doblhammer, PhD; Britta Haenisch, PhD

Data on Risk of Incident Dementia by PPI Use

Risk Factor	Risk of Incident Dementia: Both Sexes HR (95% CI)	P Value	Male Sex HR (95% CI)	P Value	Female Sex HR (95% CI)	P Value
PPI use calculated[a]						
With potential confounding factors	1.44 (1.36-1.52)	<.001	1.52 (1.33-1.74)	<.001	1.42 (1.33-1.51)	<.001
Without potential confounding factors	1.66 (1.57-1.76)	<.001	1.78 (1.56-2.03)	<.001	1.61 (1.52-1.71)	<.001
Age[b]	1.083 (1.081-1.085)	<.001	1.089 (1.084-1.093)	<.001	1.081 (1.079-1.084)	<.001
Sex[c]	1.15 (1.11-1.18)	<.001				
Depression	1.28 (1.24-1.32)	<.001	1.54 (1.41-1.68)	<.001	1.24 (1.20-1.29)	<.001
Diabetes	1.05 (1.02-1.08)	<.001	1.08 (1.02-1.14)	.01	1.04 (1.01-1.07)	.01
Stroke	1.37 (1.29-1.46)	<.001	1.63 (1.45-1.82)	<.001	1.29 (1.19-1.39)	<.001
Ischemic heart disease	0.93 (0.91-0.95)	<.001	0.91 (0.86-0.96)	<.001	0.94 (0.91-0.96)	<.001
Polypharmacy[d]	1.16 (1.13-1.19)	<.001	1.16 (1.10-1.22)	<.001	1.16 (1.13-1.19)	<.001

Abbreviations: HR, hazard ratio; PPI, proton pump inhibitor.
[a] Use of PPI before the diagnosis of dementia.
[b] At the beginning of the study in 2004.
[c] Male sex as reference.
[d] Defined as the administration of 5 or more drugs.

JAMA Neurol. doi:10.1001/jamaneurol.2015.4791
Published online February 15, 2016.



PPI refractory GERD

- rapid metabolisation
  - CYP 2C19 polymorphism
- inadequate dosing

what are the alternatives?

GERD

New drugs
New devices

The binding selectivity of vonoprazan (TAK-438) to the gastric H^+,K^+-ATPase

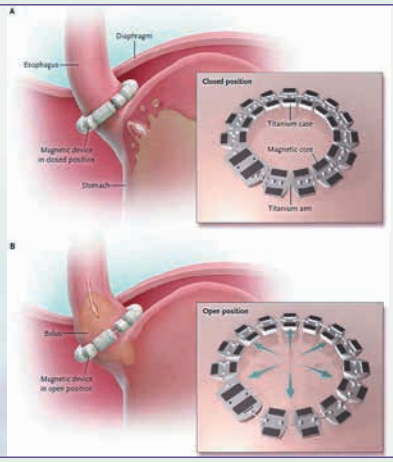
D. R. Scott*,†, K. B. Munson*,‡, E. A. Marcus*,§, N. W. G. Lambrecht¶ & G. Sachs*,†,‡

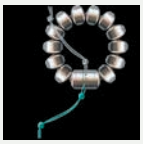
Aliment Pharmacol Ther. 2015 Sep 30.

A new alternative to PPIs is the pyrrolo-pyridine, vonoprazan (TAK-438), a potassium-competitive acid blocker (PCAB).

Vonoprazan binds selectively to the parietal cell, independent of acid secretion.

Slow dissociation from the H+ ,K+ -ATPase and long-lasting inhibition.





Magnetic Device for Augmentation of the Lower Esophageal Sphincter.

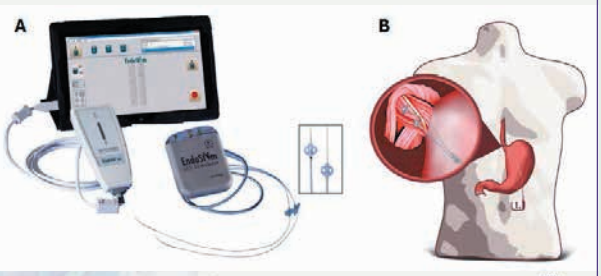
Ganz, *et al.* N Engl J Med. 2013 Feb 21; 368(8): 719–27.

Esophageal Sphincter Device for Gastroesophageal Reflux Disease

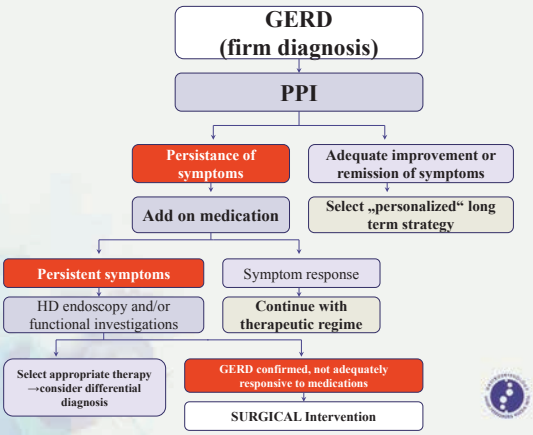
- 100 patients with gastroesophageal reflux disease before and after sphincter augmentation
- Normalization of acid exposure was achieved in 64% of patients (95% confidence interval [CI], 54 to 73). For the secondary outcomes, a reduction of 50% or more in the use of proton-pump inhibitors occurred in 93% of patients

Ganz, *et al.* N Engl J Med. 2013 Feb 21; 368(8): 719–27.

Lower esophageal sphincter stimulation system



Soffer, *et al.* World J Gastrointest Pharmacol Ther 2016 February 6; 7(1): 145–155.



THE NON-EROSIVE FORM OF GERD – A MODERN UNDERSTANDING OF THE PROBLEM AND APPROACHES TO TREATMENT

Alexander S. TRUKHMANOV

Sechenov First Moscow State Medical University; Internal Diseases Propaedeutic, Gastroenterology, Hepatology Department; Secretary General of Russian Gastroenterological Association; ESNM Steering Committee Councillor; Pogodinskaya 1/1, Moscow; Russian Federation

Non-erosive reflux disease (NERD) is the most frequent phenotypic manifestation of gastroesophageal reflux disease (GERD). NERD is a subcategory of GERD which is characterized by pronounced reflux-related symptoms (due to acid, weakly acidic or weakly alkaline reflux) with no erosions in the esophageal mucosa at the typical endoscopy and with no acid-suppressive therapy. However, these patients are distinctly heterogeneous from the pathophysiological point of view. The pronouncement of the symptoms does not allow steadily differentiating NERD and the erosive form of GERD. Therapy by H_2 antagonists or PPIs, including therapy performed by the patient on his/her own, may interfere of the endoscopic diagnostics of erosions in the esophagus. Though reflux of hydrochloric acid is the most important cause of symptom occurrence in patients with NERD, the symptoms may also be associated with non-acid or weakly acidic reflux. Combined impedance-pH monitoring allows revealing a temporary association between reflux episodes and symptom occurrence what has a significant importance for NERD diagnostics. Using this method, patients with NERD may be differentiated into two groups (with pathological acid reflux and hypersensitive esophagus) and separated from patients with so called functional heartburn (in whom symptoms are not related to any reflux and who should be excluded from the GERD category). Pathophysiological mechanisms of NERD symptom formation are not completely explained but the presence of a microscopic esophagitis, including dilatation of intercellular spaces is the most likely to play the corresponding role. Among supposed mechanisms, mucosal hypersensitivity and mechanical stimulation of a large volume of refluxate are also present. Patients with NERD in whom reflux of hydrochloric acid is the main pathogenic factor, respond to PPI therapy very well. Therapeutic efficacy of a course of empiric therapy with PPIs in the usual dose should be estimated 2 to 4 weeks after the treatment, but for some patients the course may take up to 12 weeks to obtain the effect. Persistent symptoms of reflux at an adequate antisecretory treatment for more than 12 weeks require an additional examination. Inefficacy of PPI therapy requires, first of all, control of the respect of guidelines for the lifestyle change and the medication administration. For patients with a hypersensitive esophagus and weakly acidic or weakly alkaline reflux, it is necessary to set out the prescription of prokinetic agents.

alexander.trukhmanov@gmail.com

Trukhmanov A.S. The non-erosive form of GERD – A modern understanding of the problem and approaches to treatment. In: *11th International Symposium of Gastroenterology, Saint Petersburg, Russia, 12–14 May 2016*. [online].
Available from URL: http://www.promedcs.eu/sites/default/files/abstractbook_2016.pdf

GERD COMPLICATIONS: BARRETT'S METAPLASIA AND OTHERS. RECOMMENDATION FOR CLINICAL PRACTICE

Radek KROUPA

Department of Internal Medicine and Gastroenterology, University Hospital and Faculty of Medicine, Masaryk University, Brno; Czech Republic

Long term esophageal exposure to gastric content in untreated and non-optimally treated patients with gastroesophageal reflux disease (GERD) may develop in important complications. In addition to relief of symptoms, the clinical management of GERD should be focused on prevention of esophageal ulcers with risk of bleeding, peptic stricture, intestinal metaplasia of the esophageal mucosa – Barrett's esophagus and subsequent development of dysplasia and adenocarcinoma. Chronic extraesophageal symptoms are troublesome complications of GERD in some patients too. For the complex clinical view, it is necessary to take in account the risk of chronic acid suppressive treatment and anti-reflux surgery complications.

Metaplasia of the squamous epithelium to the columnar type with intestinal differentiation is a result of chronic exposure (more than 8–10 years?) of esophageal mucosa to gastroduodenal contents. Diagnosis of Barrett's esophagus (BE) is based on both histological confirmation of specialized intestinal metaplasia with goblet cells and characteristic features on endoscopy – mucosal tongues or an upward shift of squamocolumnar junction. The fear of BE is correlated with an increased risk of development of esophageal adenocarcinoma (EAC). Estimated risk of adenocarcinoma is about 1 patient from 500–800 patients with BE per year. Patients with BE may report reflux symptoms, usually more in history than in presence. Screening for BE among all patients with reflux symptoms is controversial. Long term reflux symptoms, age over 50, male sex, smoking and obesity are commonly recognized risk factors and may be triggers for endoscopic screening. The prevalence of Barrett's esophagus in general adult population is about 1–2% and up to 10% in patients with symptoms of gastroesophageal reflux.

Treatment of GERD may prevent the development of BE. All patients with BE should treated by proton pump inhibitor for control of GERD symptoms. Aggressive PPI dosing is not generally recommended. Fundoplication has a role for control of reflux symptoms either esophageal or extraesophageal, but it is not recommended for purpose of prevention of neoplastic progression of BE. Endoscopic surveillance with biopsies is generally recommended in patients with BE. Effect of such surveillance program may be consider in view of appreciated yield in individual patient. Major guidelines suggest endoscopic surveillance every 3–5 years in patients without dysplasia, or every 2–3 years if segment length is more than 3 cm. The overall risk of development of esophageal cancer do not exceed 0.5% per patient-year. There is no clear evidence for efficacy of surveillance in reducing risk of mortality due to esophageal cancer.

PPI use may be associated with decreased risk of progression of BE to adenocarcinoma or high grade dysplasia. PPI use may increase risk of fractures, bacterial infections, vitamin and nutrients deficiency. Chemoprevention is not recommended for patients with Barrett's esophagus. There is insufficient evidence to support use of aspirin, NSAIDs or other

chemopreventive agents. There is very mild evidence than antireflux surgery might reduce risk of esophageal adenocarcinoma compared to medical treatment in patients with BE. The risk of esophageal adenocarcinoma is still substantially increased (10 times) in operated patients compared to general population and surveillance program should be continued. Decision making between medical or surgical long term management of GERD to prevent the development of carcinoma is controversial. There is lacking sufficient evidence to prefer any of this methods obviously.

Endoscopic resection should be indicated for Barrett's related neoplasia associated with visible lesions. Resection of all visible lesions serves as most accurate staging intervention. Cap and snare technique with submucosal injection and band ligation technique are considered to be equally effective. Radifrequency ablation is recommended for all residual BE segment after endoscopic resection of granular/suspicious parts or for flat segment with high and low grade dysplasia. No endoscopic intervention is indicated in patients without dysplasia.

Tab. Summary of considered surveillance and intervention in BE.

New diagnosis of BE	confirmation of BE within 1 year from initial endoscopy with careful inspection of mucosa and extensive biopsies	
	surveillance	interventions
BE without dysplasia	every 3–5 years every 2–3 years for long segment BE (3 cm)	No
BE with low grade dysplasia	every 6–12 months (confirmed LGD on repeated endoscopy and by specialized pathologist)	only endoscopic surveillance or mucosal resection of visible abnormal parts and radiofrequency ablation (RFA) or other ablative method (hybrid APC, PDT)
BE with high grade dysplasia or adenocarcinoma limited to mucosa	intensive surveillance 3 m??? (only in limited cases due to patient wishes)	endoscopic eradication therapy: endoscopic mucosal resection ablative RFA, photodynamic therapy (PDT) or esophagectomy

Peptic strictures due to chronic esophageal reflux injury and subsequent fibrous tissue formation are the most common causes of benign esophageal strictures and organic dysphagia. These strictures are typically short and most occur in the distal part of the esophagus on the border between tubular and squamous epithelium including Barrett's metaplasia. The goal of therapy is to resolve dysphagia and reduce recurrence of stricture formation. Esophageal dilations under endoscopy or Xray control (using balloon or bougie dilators) should be accompanied with effective acid suppressive therapy.

Selected references:

1. Shaheen N.J., Falk G.W., Iyer P.G., Gerson L.B. ACG Clinical Guideline: Diagnosis and Management of Barrett's Esophagus. Am J Gastroenterol. 2016; 111(1): 30–50.
2. NICE guideline on dyspepsia and gastro-oesophageal reflux disease (National Guideline Clearinghouse 2015 Mar 2).
3. de Jonge P.J.F., van Blankenstein M., Grady W.M., *et al.* Barrett's oesophagus: epidemiology, cancer risk and implications for management. Gut 2014; 63: 191–202.
4. Maret-Ouda J., Konings P., Lagergren J., Brusselaers N. Antireflux Surgery and Risk of Esophageal Adenocarcinoma: A Systematic Review and Meta-analysis. Ann Surg. 2016; 263(2): 251–257.

Supported by Ministry of Health, Czech Republic – conceptual development of research organization (FNBr, 65269705).

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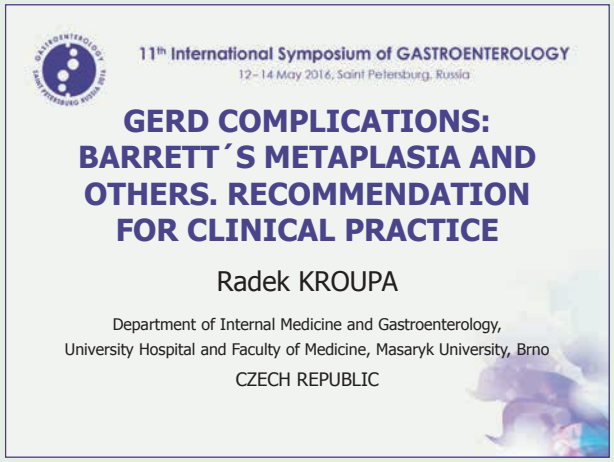
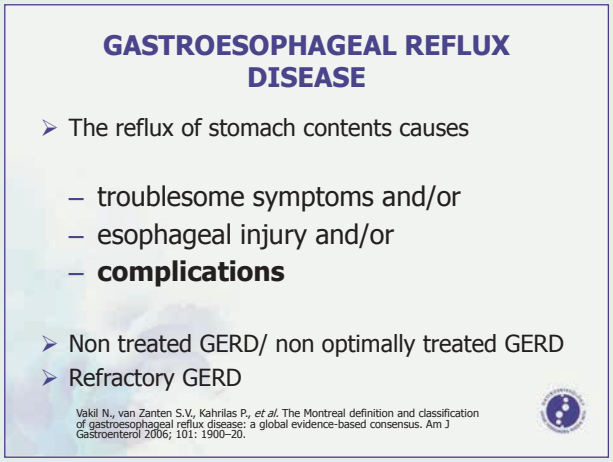
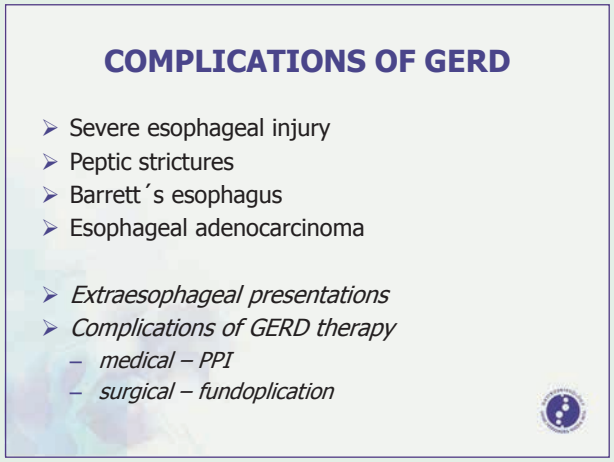
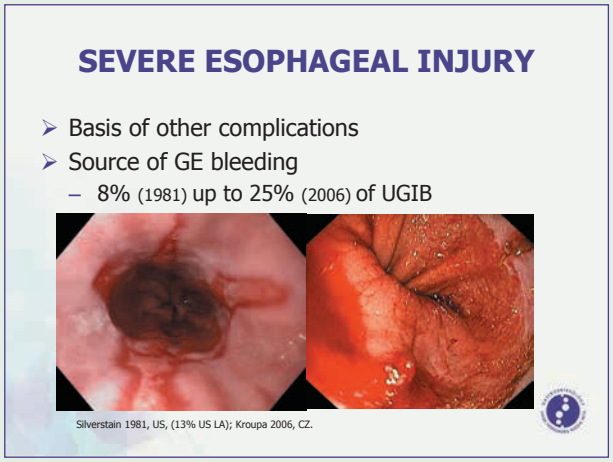






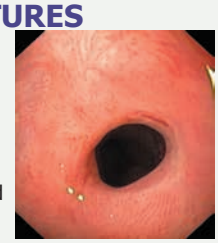


SEVERE ESOPHAGEAL INJURY

- Prolonged and high dose PPI treatment
- Repeat endoscopy after 2–3m: mucosal healing, detection of Barrett´s esophagus
- Long term maintenance therapy often needed
- Compliance, lifestyle modification
- Consider antireflux surgery?

Modiano N., Gerson L.B. Risk factors for the detection of Barrett's esophagus in patients with erosive esophagitis. Gastrointest Endosc 2009; 69: 1014–20.

PEPTIC STRICTURES

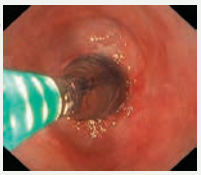


- Fibrous tissue formation
- Most common benign esophageal strictures
- On the border between tubular and squamous epithelium (cardia, BE)
- Different regional prevalence 3,7%(RU)–0,8%(CZ) decreasing incidence
  - elderly, Barrett´s esophagus, recurrent strictures

Vasilevskíi D., Skurikhin S., Bagnenko S., *et al.* Prevalence of erosive esophagitis and peptic esophageal strictures. Khirurgiia 2015; (6): 35–37. Kroupa. unpublished data 2016.

PEPTIC STRICTURES

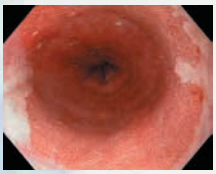
- Balloon dilatation, bougie dilatation
- Concomitant high dose PPI therapy
- Local corticosteroid injection
- Selfexpanding removable stents
  - Non optimal results
- Recurrent dilatation procedures

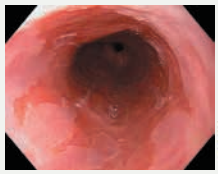


Dan D. Removable esophageal stents have poor efficacy for the treatment of refractory benign esophageal strictures (RBES). Diseases Of The Esophagus 2014; 27 (6): 511–517. Pregun I., Hritz I., Tulassay Z., Herszényi L. Peptic esophageal stricture: medical treatment. Digestive Diseases 2009; 27 (1): 31–37.

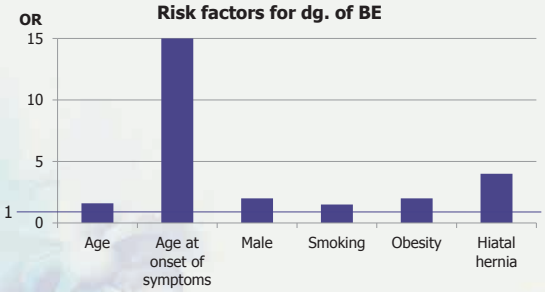
BARRETT´S ESOPHAGUS

- Replacement of normal squamous epithelium in distal esophagus by specialized intestinal metaplasia
- Detected in 6–15% patients with GERD symptoms (long segment BE up to 3%)



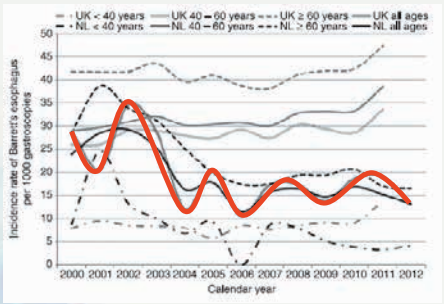


BARRETT´S ESOPHAGUS



Shaheen N. ACG Clinical Guideline: Am J Gastroenterol 2015. Thrift A. Age at onset of GERD symptoms predicts risk of BE. Am J Gastroenterol 2013.

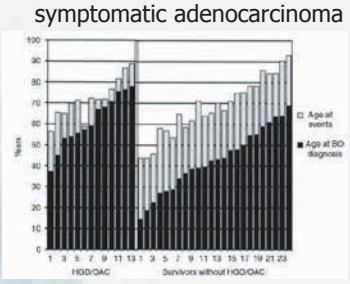
INCIDENCE OF BARRETT´S ESOPHAGUS IN GASTROSCOPIES



Masclee, G.M.C. Aliment Pharmacol Ther 2014; 39: 1321–1330.

INCUBATION PERIOD

- Approx.. 15-30 years period from the onset of Barrett's esophagus to development of symptomatic adenocarcinoma



den Hoed, C.M. *et al.* British Journal of Cancer (2011).

EPIDEMIOLOGY OF BE

- Screening of BE?
- Risk population:
  - Men with chronic GERD symptoms (> 5 years) +
  - Age > 50
  - Central obesity
  - Smoking
  - Family history of BE or EAC
- Repeating endoscopic evaluation? 8–10 years?

GOALS *(WISHES)* OF MANAGEMENT OF PATIENTS WITH BE

- **To reduce risk of development of esophageal adenocarcinoma (EAC)**
- **To reduce mortality for EAC**

- To treat dysplasia to stop development of cancer
- To perform surveillance and therapy effectively and safely
- Do not frighten patients by high risk of cancer

PROGRESSION OF BE TO EAC

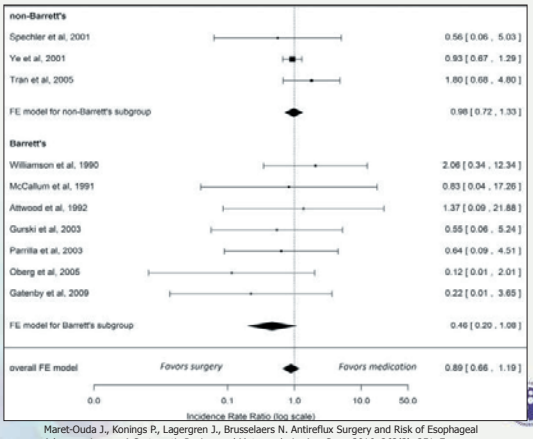
Progression	patients per year
Barrett´s esophagus (all) do EAC	0.2–0.5%
Non-dysplastic BE to LGD	4.3%
Non-dysplastic BE to EAC	0.12–0.6%
Low grade dysplasia (LGD) to EAC	0.5–1%
High grade dysplasia (HGD) do EAC	4–7%

Sharma P., Falk G.W., Weston A.P., *et al.* Dysplasia and cancer in a large multicenter cohort of patients with Barrett's esophagus. Clin Gastroenterol Hepatol 2006; 4: 566–572. Hvid-Jensen, F.N. Engl J Med 2011; 365: 1375–1383. Singh, S. Gastrointest Endosc 2014; 79: 897–909.

MANAGEMENT OF BE

- **Antireflux therapy**
  - PPI – standard dosing / drugs equal
  - Antireflux surgery – fundoplication
  - Equally efficient / surgery may slightly reduce the risk of development EAC
- **Surveillance**
  - Independently on type of antireflux therapy
  - Biopsies, protocol, time periods

Maret-Ouda J., Konings P., Lagergren J., Brusselaers N. Antireflux Surgery and Risk of Esophageal Adenocarcinoma: A Systematic Review and Meta-analysis. Ann Surg. 2016; 263(2): 251–7.



Maret-Ouda J., Konings P., Lagergren J., Brusselaers N. Antireflux Surgery and Risk of Esophageal Adenocarcinoma: A Systematic Review and Meta-analysis. Ann Surg. 2016; 263(2): 251–7.

MANAGEMENT OF DYSPLASTIC BE AND CANCER

- **Endoscopic therapy**
  - Endoscopic mucosal resection for nodularity
  - Ablative therapy for residual segment in HGD/LGD (RFA, APC, PDT)
  - Therapy of superficial EAC – T1a
- **Surgery**
  - Esophagectomy for deeper invasive EAC
  - Neoadjuvant multimodal therapy

Shaheen N. ACG Clinical Guideline. Am J Gastroenterol 2015. Fitzgerald R.C. British Society of Gastroenterology guidelines on the diagnosis and management of Barrett's esophagus. Gut. 2014; 63(1): 7–42. Martínek, J. Standardy České gastroenterologické společnosti – endoskopická léčba pacientů s Barrettovým jícnem a časnými neoplaziemi jícnu. Gastroenterologie a Hepatologie 2013, 67(6): 479–487.

SURVEILLANCE IN BE

New diagnosis of BE	**Confirmation of BE within 1 year from initial endoscopy with careful inspection of mucosa and extensive biopsies**

Shaheen N. ACG Clinical Gudeline. Am J Gastroenterol 2015. Fitzgerald R.C. British Society of Gastroenterology guidelines on the diagnosis and management of Barrett's esophagus. Gut. 2014; 63(1): 7–42.

SURVEILLANCE IN BE

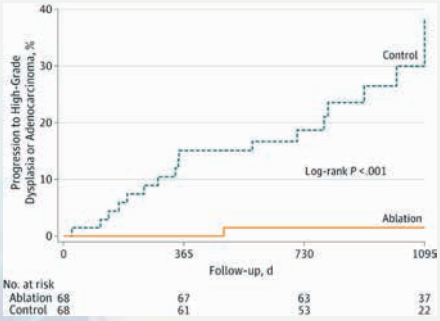
	Surveillance endoscopy	Interventions
BE without dysplasia	- every 3-5 years - every 2-3 years for long segment BE (3cm)	No

Shaheen N. ACG Clinical Gudeline. Am J Gastroenterol 2015. Fitzgerald, R.C. British Society of Gastroenterology. British Society of Gastroenterology guidelines on the diagnosis and management of Barrett's esophagus. Gut. 2014; 63(1): 7–42.

SURVEILLANCE IN BE

	Surveillance endoscopy	Interventions
BE with low grade dysplasia (LGD)	every 6–12 months (confirmed LGD on repeated endoscopy and by specialized pathologist)	Only endoscopic surveillance **or** Mucosal resection of visible abnormal parts And Ablative method (Radiofrequence ablation, Argon plasma coagulation, PDT)

RFA FOR LOW GRADE DYSPLASIA BARRETT´S ESOPHAGUS



Phoa K. *et al.* Radiofrequency Ablation vs Endoscopic Surveillance for Patients With Barrett Esophagus and Low-Grade Dysplasia: A Randomized Clinical Trial. JAMA 2014; 311(12): 1209–1217.

SURVEILLANCE IN BE

	Surveillance	Interventions
BE with high grade dysplasia (HGD) or EAC limited to mucosa	intensive surveillance 3m??? (only in limited cases with HGD due to patient wishes)	**Endoscopic eradication therapy:** Endoscopic mucosal resection + Ablative therapy Or Esophagectomy

Shaheen N. ACG Clinical Gudeline. Am J Gastroenterol 2015. Fitzgerald R.C. British Society of Gastroenterology guidelines on the diagnosis and management of Barrett's esophagus. Gut. 2014; 63(1): 7–42.

ENDOSCOPIC MUCOSAL RESECTION

- All visible abnormalities
- Biopsy sampling – accurate staging
- Cap assisted, ligator assisted – equally effective
- Risk of stricture formation

Shaheen N. ACG Clinical Gudeline. Am J Gastroenterol 2015. Fitzgerald R.C. British Society of Gastroenterology guidelines on the diagnosis and management of Barrett's esophagus. Gut. 2014; 63(1): 7–42.

ENDOSCOPIC ABLATIVE METHODS

- **Radiofrequency ablation** (HALO 360, 90)
  - Encouraging results – elimination of IM
  - Decreased risk of development of EAC
  - Repeated sessions needed
  - Absence of histology samples
  - Risk of stricture formation (10–15%)
  - Costs

- **Argon plasma coagulation** (hybrid)
- **Photodynamic therapy**

Shaheen N. ACG Clinical Gudeline. Am J Gastroenterol 2015. Fitzgerald R.C. British Society of Gastroenterology guidelines on the diagnosis and management of Barrett's esophagus. Gut. 2014; 63(1): 7–42.

CLINICAL PROBLEMS

- Intestinal metaplasia in very short segment of visible metaplastic mucosa (< 1 cm)
- Quality of endoscopy, quality of pathological diagnosis
- Availability and costs of therapeutic endoscopy – EMR, RFA, others
- Relativity of esophageal cancer burden to colorectal cancer (screening programs)

SUMMARY

- GERD therapy may prevent development of Barrett´s esophagus and other complications
- Guidelines recommend surveillance intervals and interventions
  - Consider endoscopic intervention in LGD
  - HGD should be treated endoscopically
- New therapeutic methods make evolution in approach to patients with BE, but endoscopical surveillance cannot be omitted

GERD IN PATIENTS WITH METABOLIC SYNDROME

Igor MAEV[1], Tatiana LAPINA[2]

1. A. I. Yevdokimov Moscow State University of Medicine and Dentistry, Moscow. 2. Vasilenko Clinic of internal diseases propedeutics, gastroenterology and hepatology, Sechenov First Moscow State Medical University, Moscow; Russian Federation

Metabolic syndrome (MS) is a complex of metabolic, hormonal and clinical disorders that are risk factors for development of a number of socially important diseases. In clinical practice, the main sign of MS is obesity where waist circumference is more than 80 cm in women and more than 94 cm in men, combined with other criteria of this syndrome: hypertension, increase in TSH, decrease in HDL cholesterol, increase in LDL cholesterol, fasting hyperglycemia, and impaired glucose tolerance. Morbidity of MS is growing in parallel with the growth of obesity in population (1). From current point of view, obesity is a chronical metabolic disease developing because of imbalance of energy consumption and expenditure, manifested as overdevelopment of adipose tissue, progressing at the natural course, having specific complications, increasing the different diseases risk, and having a high probability of recurrence after the end of a treatment course (2).

Currently, it is stated that obesity is one of the leading risk factors for gastroesophageal reflux disease (GERD), a pathology which is characterized by spontaneous or regularly repeated reflux of gastric or duodenal content in the esophagus (3–5). Pathogenic mechanisms underlying the connection between obesity, MS and GERD are not definitely revealed. It is assumed that obesity increases the possibility of spontaneous relaxations of the lower esophageal sphincter, associated with GERD. Besides, visceral obesity at MS leads to higher abdominal pressure which provokes, in its turn, GERD formation due to higher gastric pressure. At overweight, esophageal motility disorders may also participate in the genesis of GERD, accompanied by decreased esophageal acid clearance (6).

In patients with MS and obesity, the classical symptom of GERD, heartburn, occurs less frequently than in people with the normal trophological status. Nevertheless, the risk of extra-esophageal symptoms and complications of GERD in patients with overweight and obesity is higher (7–8). Weight correction in patients with GERD and MS is an important factor in treatment and control of disease symptoms. At present, the main principles of the treatment of GERD are considered as follows: the need of prescription of proton pump inhibitors and prokinetic agents, and long principal (at least 4–8 weeks) and supporting (6–12 months) therapies (9). It is important to note that in patients with overweight and obesity due to heterogeneous variety of different mechanisms, alteration of pharmacokinetic profile of administrated medications may occur that may impact their efficacy.

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1. Shen J., Goyal A., Sperling L. The emerging epidemic of obesity, diabetes, and the metabolic syndrome. Cardiol Res Pract. 2012; Article ID: 178675.
2. Castro A.V., Kolka C.M., Kim S.P., Bergman R.N. Obesity, insulin resistance and comorbidities? Mechanisms of association. Arq Bras Endocrinol Metabol. 2014; 58(6): 600–609.

3. Serag H. Time trends for gastroesophageal reflux disease: A systematic review. Clin Gastroenterol Hepatol. 2007; 5: 17–26.
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5. Hajar N., Castell D.O., Ghomrawi H., *et al*. Impedance pH confirms the relationship between GERD and BMI. Dig Dis Sci 2012; 57: 1875–1879.
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9. Maev I.V., Andreev D.N., Dicheva D.T. Gastroesophageal reflux disease: from pathogenesis to therapeutic aspects//Consillium Medicum. 2013; 8: 30–34.

Maev I., *et al*. GERD in patients with metabolic syndrome. In: *11th International Symposium of Gastroenterology, Saint Petersburg, Russia, 12–14 May 2016*. [online].
Available from URL: http://www.promedcs.eu/sites/default/files/abstractbook_2016.pdf

11th International Symposium of GASTROENTEROLOGY
12–14 May 2016, Saint Petersburg, Russia

GERD IN PATIENTS WITH METABOLIC SYNDROME

Tatiana LAPINA
Chair of internal diseases propedeutics, Vasilenko Clinic of internal diseases propedeutics, gastroenterology and hepatology
I.M. Sechenov First Moscow State Medical University
RUSSIAN FEDERATION

GERD AND OBESITY

GERD AND OBESITY

- N=1524
- BMI >30 kg/m^2 (OR = 2.8; CI, 1.7 to 4.5)
- reporting an immediate family member with heartburn or disease of the esophagus or stomach (OR = 2.6; CI, 1.8 to 3.7)
- a past history of smoking (OR = 1.6; CI, 1.1 to 2.3)
- consuming more than seven drinks per week (OR = 1.9; CI, 1.1 to 3.3)

Locke GR, Talley NJ, Fett SL et al. Risk factors associated with symptoms of gastroesophageal reflux. Am J Med. 1999;106: 642-9.

- N=435
- Obese participants were 2.5 times as likely as those with normal BMI (<25) to have reflux symptoms or esophageal erosions.

El-Serag HB et al. Obesity is an independent risk factor for GERD symptoms and erosive esophagitis. Am J Gastroenterol. 2005;100(6):1243-50.

GERD AND OBESITY

BMI >30 kg/m^2 compared with BMI<25 kg/m^2

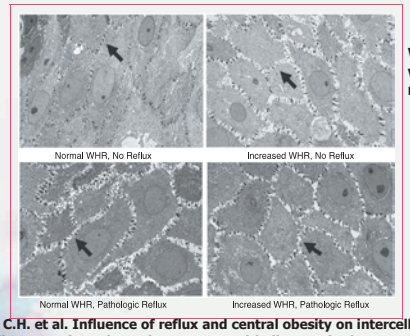
- ↑acid reflux episodes
- ↑long reflux episodes (>5 min)
- ↑time with pH<4

El-Serag HB, Ergun GA, Pandolfino J, et al. Obesity increases oesophageal acid exposure. Gut 2007; 56: 749–755.

- ↑Oesophageal acid exposure (WC: R = 0.284, P < 0.001)
- ↓Lower oesophageal sphincter (LOS) pressure
- ↓Abdominal LOS length
- ↑Peristaltic dysfunction (all P < 0.001)

Anggiansah R et al. The effects of obesity on oesophageal function, acid exposure and the symptoms of gastro-oesophageal reflux disease. Aliment Pharmacol Ther. 2013;37(5):555-63.

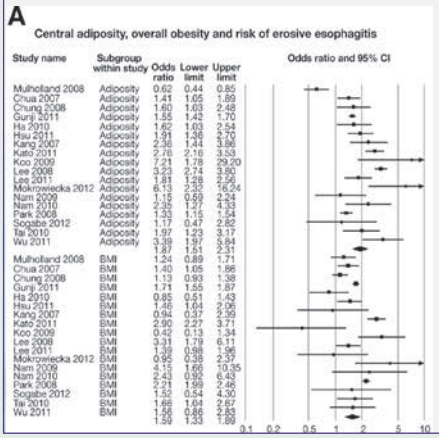
CENTRAL OBESITY POTENTIATES REFLUX-INDUCED ESOPHAGEAL INJURY AND INFLAMMATION



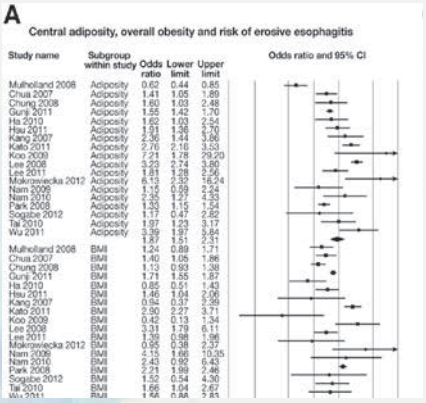
WHR - waist-to-hip ratio

Blevins C.H. et al. Influence of reflux and central obesity on intercellular space diameter of esophageal squamous epithelium. United European Gastroenterology Journal. 2016, Vol. 4(2) 177–183

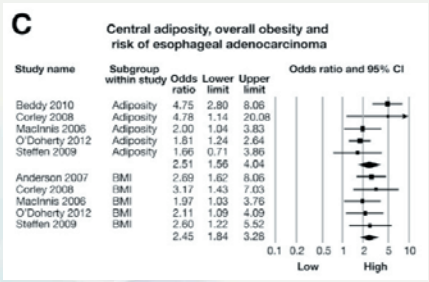
OBESITY AND BARRETT'S ESOPHAGUS (BE)/ ESOPHAGEAL ADENOCARCINOMA (EAC)



Singh S et al. Central adiposity is associated with increased risk of esophageal inflammation, metaplasia, and adenocarcinoma: a systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2013;11(11):1399-1412



Singh S et al. Central adiposity is associated with increased risk of esophageal inflammation, metaplasia, and adenocarcinoma: a systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2013;11(11):1399-1412



Singh S et al. Central adiposity is associated with increased risk of esophageal inflammation, metaplasia, and adenocarcinoma: a systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2013;11(11):1399-1412

HIGHER CHILDHOOD BMI ELEVATED RISK OF OESOPHAGEAL ADENOCARCINOMA IN ADULT

- Copenhagen School Health Records Register - analyses included 255 053 children born during 1930-1971
- Danish Cancer Registry
- 254 (216 - males) – oesophageal adenocarcinoma
- High BMI in et age of 9-13 years – significant risk factor of EAC

Cook MB et al. Childhood body mass index in relation to future risk of oesophageal adenocarcinoma. Br J Cancer. 2015;112(3):601-7.

Table 1. Single nucleotide polymorphisms included in the genetic risk score for body mass index

Chr	Nearest gene	SNP	Risk allele*	Other allele	Frequency of risk allele	Per allele change in BMI†
1	NEGR1	rs2815752	T	C	0.62	0.13
	TNNI3K	rs1514175	A	G	0.43	0.07
	PTBP2	rs10489741	T	C	0.58	0.06
	SEC16B	rs543874	G	A	0.20	0.22
2	TMEM18	rs2867125	C	T	0.82	0.31
	ADCY3, RBJ	rs713587	A	G	0.49	0.14
	FANCL	rs2192497	G	A	0.29	0.10
3	CADM2	rs13078807	C	T	0.22	0.10
4	GNPDA2	rs10938397	G	A	0.43	0.18
	SLC39A8	rs13107325	A	G	0.08	0.19
5	FLJ35779	rs10057967	A	G	0.64	0.10
	ZNF608	rs4836133	A	G	0.43	0.07
6	TFAP2B	rs987237	C	T	0.19	0.13
	NUDT3	rs206936	C	T	0.19	0.06
9	LRRN6C	rs10968576	G	A	0.32	0.11
11	STK33, RPL27A	rs11041994	C	A	0.52	0.06
	BDNF	rs7103411	T	C	0.77	0.19
	CELF1, MTCH2	rs7124681	T	G	0.47	0.06
12	BCDIN3D, FAIM2	rs7138803	A	G	0.39	0.06
13	MTIF3, GTF3A	rs9512699	G	A	0.20	0.08
14	NRXN3	rs17109256	T	C	0.22	0.10
15	MAP2K5	rs2241423	C	T	0.79	0.13
16	GPRC5B, IQCK	rs12444979	G	A	0.86	0.12
	SH2B1	rs7498665	C	T	0.40	0.15
	FTO	rs9930506	G	A	0.42	0.39
18	MC4R	rs571312	T	G	0.23	0.23
19	KCTD15	rs29942	G	A	0.68	0.06
	QPCTL	rs2287019	C	T	0.80	0.08
	ZC3H4, TMEM160	rs3810291	T	C	0.66	0.06

Speliotes EK, Willer CJ, Berndt SI, et al. Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. Nat Genet. 2010;42(11):937–948

N=250000 – 32 SNPs

GENETIC ASPECT

- 2061 BE patients, 999 EAC patients, 2169 – контроль
- Using 29 of the 32 BMI-associated SNPs from the GIANT GWAS study, a genetic risk score (GRS) was calculated for each subject based on the total number of alleles (zero, one, or two) present for each of the BMI-associated SNPs (0/1/2)
- Weighted GRS - the relative contribution of each of the SNPs to BMI
- EAC risk increased by 16% and BE risk increased by 12% per 1kg/m^2 increase in BMI

Thrift AP et al. Obesity and risk of esophageal adenocarcinoma and Barrett's esophagus: a Mendelian randomization study. Natl Cancer Inst. 2014;106(11).

GERD AND METS

GERD AND METS

- Cross-sectional study
- N=100 consecutive patients who underwent a 24-hour pH-metry monitoring and were assessed for the five MetS components
- N=54 GERD/ N=46 GERD-free patients
- Frequency of metabolic syndrome as a whole entity was higher among patients with GERD than those without GERD (50 vs. 19.56%; P= 0.002) with a crude odds ratio of 4.11 (95% CI: 1.66-10.14)

Kallel L et al. Metabolic syndrome is associated with gastroesophageal reflux disease based on a 24-hour ambulatory pH monitoring. Dis Esophagus. 2011;24(3):153-9

GERD AND INSULIN RESISTANCE

- N=743
- Gastro-oesophageal reflux questionnaire, fasting insulin data, endoscopy, homeostatic model assessment-insulin resistance (HOMA-IR) index
- Older age, male gender, smoking and alcohol consumption increased the prevalence of EO, but not GERD symptoms.
- A large waist circumference, high fasting blood glucose levels and high number of metabolic syndrome components were associated with increased prevalence of both EO and GERD symptoms, while high blood pressure was associated with increased prevalence of EO only.
- Higher scores in the gastro-oesophageal reflux questionnaire were associated with higher HOMA-IR index, and higher HOMA-IR index was associated with increased prevalence of EO (adjusted odds ratio 1.14, 95% CI 1.03-1.26, P = 0.012).

Hsu CS et al. Increasing insulin resistance is associated with increased severity and prevalence of gastro-oesophageal reflux disease. Aliment Pharmacol Ther. 2011;34(8):994-1004

GERD AND NAFLD

GERD AND NAFLD

- Cross-sectional study
- N=206 outpatients diagnosed with NAFLD and 183 controls
- The prevalence of GERD symptoms was higher in NAFLD patients than controls (61.2 vs. 27.9%, p < 0.001).
- Positive association between NAFLD and the experiencing of heartburn, regurgitation and belching.
- GERD symptoms were related to BMI and MetS

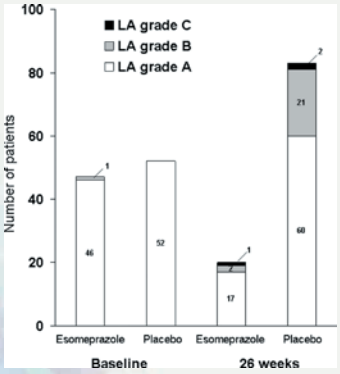
Catanzaro R. et al. Nonalcoholic fatty liver disease increases risk for gastroesophageal reflux symptoms. Dig Dis Sci. 2014;59(8):1939-45.

REDUCING THE RISK OF GASTRIC AND/OR DUODENAL ULCERS IN PATIENTS RECEIVING CONTINUOUS, LOW-DOSE ASPIRIN THERAPY

- **> or =60 yr**
- **without baseline gastroduodenal ulcer at endoscopy**
- **aspirin 75-325 mg once daily**
- **eso 20 mg N = 493; placebo N = 498**
- **Endoscopy at weeks 8 and 26**
- **Upper gastrointestinal symptoms at weeks 8, 16, and 26**
- **27 patients (5.4%) in the placebo group developed a gastric or duodenal ulcer during 26 weeks' treatment compared with 8 patients (1.6%) in the esomeprazole group**
- **life-table estimates: 6.2% vs 1.8%; P= 0.0007**

Yeomans N., Lanas A., Labenz J. et al. Efficacy of esomeprazole (20 mg once daily) for reducing the risk of gastroduodenal ulcers associated with continuous use of low-dose aspirin. // Am J Gastroenterol. 2008;103(10):2465-73.

ASPIRIN AND GERD



Erosive esophagitis: 18,3% vs 4,4% (P < 0.0001)

Yeomans N., Lanas A., Labenz J. et al. Efficacy of esomeprazole (20 mg once daily) for reducing the risk of gastroduodenal ulcers associated with continuous use of low-dose aspirin. // Am J Gastroenterol. 2008;103(10):2465-73.

PREVENTION OF ASPIRIN-INDUCED GI INJURY

Rebamipide

- **Tozawa K et al. A randomized, double-blind, placebo-controlled study of rebamipide *for gastric mucosal injury* taking aspirin with or without clopidogrel. Dig Dis Sci. 2014;59(8):1885-90.**
- **Watanabe T. et al. A multicenter, randomized, double-blind, placebo-controlled trial of high-dose rebamipide treatment for low-dose aspirin-induced moderate-to-severe *small intestinal damage*. PLoS One. 2015;10(4):e0122330.**
- **Zhang S et al. Rebamipide helps defend against nonsteroidal anti-inflammatory drugs induced *gastroenteropathy*: a systematic review and meta-analysis. Dig Dis Sci. 2013;58(7):1991-2000.**
- **Katada K. et al. Prevention by rebamipide of *acute reflux esophagitis* in rats. Dig Dis Sci. 2005;50 Suppl 1:S97-S103.**

WEIGHT LOSS AND GERD

- Weight loss was followed by decreased time with esophageal acid exposure in 2 RCTs (from 5.6% to 3.7% and from 8.0% to 5.5%)
- Weight loss reduced reflux symptoms in prospective observational studies.
- In RCTs, late evening meals increased time with supine acid exposure compared with early meals (5.2% point change), and head-of-the-bed elevation decreased time with supine acid exposure compared with a flat position (from 21% to 15%).

Ness-Jensen E et al. Lifestyle Intervention in Gastroesophageal Reflux Disease. Clin Gastroenterol Hepatol. 2016;14(2):175-82

CONCLUSION

- **It is necessary to consider GERD and BE as frequent events in metabolic syndrome patients.**
- **The risk of EAC is high in metabolic syndrome patients.**
- **Aerobic exercise and caloric reduction should be the key lifestyle modifications in metabolic syndrome patients with GERD.**

CURRENT THERAPEUTIC ARMAMENTARIUM IN CHOLESTATIC LIVER DISEASES

Marek HARTLEB

Department of Gastroenterology and Hepatology, Medical University of Silesia in Katowice; Poland

Cholestasis is an impairment of bile transport that can be caused by failure of bile secretion by the hepatocytes (canalicular cholestasis) or cholangiocytes (ductular cholestasis) or by obstruction of bile flow. The causes of cholestasis involve wide range of disorders from rare genetic diseases and disruption of the normal development of the bile excretory anatomy, to progressive, ultimately fatal diseases such as primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC). Irrespective of the etiology, hepatic retention of bile acids leads to liver injury and chronic cholestatic liver disease. Without treatment, PBC generally progresses to cirrhosis and eventually liver failure over a period of 10–20 years.

Progress in the understanding of the causes and consequences of cholestasis has provided new concepts for the medical treatment of cholestatic disorders. Therapy should address both the cause and the consequences of retained bile acids within the liver, and diminished delivery of bile to the gastrointestinal tract. Therapies should also address symptoms of chronic cholestasis, mostly pruritus and fatigue and prevention, particularly osteoporosis and osteomalacia. Portal hypertension can be an early event in chronic cholestatic liver disease, sometimes occurring before the development of cirrhosis.

The first, and currently the only approved medical treatment for PBC is ursodeoxycholic acid (UDCA). The choleretic effect of UDCA and its ability to make the bile acid pool more hydrophilic accounts for its beneficial properties. UDCA also stabilizes hepatocyte membranes, increases defence against oxidative stress, and inhibits apoptosis. When administered at doses of 13–15 mg/kg/day, UDCA is safe and well-tolerated therapy that in PBC patients improves serum biochemistry, delays progression of hepatic fibrosis and esophageal varices, and reduces likelihood of liver transplantation or death. However, the effects of UDCA in patients with PSC are limited and one out of three patients with PBC does not adequately respond to this drug, urging for development of novel therapeutic approaches. These include nuclear and membrane receptor agonists and bile acid derivatives.

Obeticholic acid (OCA) is a novel chenodeoxycholic acid derivative, which is a farnesoid X receptor agonist (FRX). Activation of FRX reduces bile acid synthesis, induces phases I and II bile acid hydroxylation and conjugation, stimulates export of alternative bile acids and limits hepatocellular bile acid import. Daily doses of OCA, ranging from 10 to 50 mg, significantly reduced levels of liver enzymes in PBC patients who had inadequate responses to UDCA. 24-norursodeoxycholic acid (norUDCA) is a side chain-modified UDCA derivative, which can undergo cholehepatic shunting and directly stimulates hypercholeresis (mainly HCO_3) protecting the liver from cholestatic injury. NorUDCA showed therapeutic effects in experimental cholestasis. Under investigation are also modifiers of retinoid X receptor (RXR), peroxisome proliferator-activated receptor α (PPARα), pregnane X receptor (PXR), and of the membrane receptors such as fibroblast growth factor receptor 4 (FGFR4) and apical sodium bile acid transporter (ASBT).

The initial step in managing fatigue and pruritus is ruling out potentially contributing factors. Despite the lack of specific therapies there are several management strategies that can be implemented to improve severity of these complications and quality of life in patients with cholestatic liver disease.

Hartleb M. Current therapeutic armamentarium in cholestatic liver diseases. In: *11th International Symposium of Gastroenterology, Saint Petersburg, Russia, 12–14 May 2016*. [online].
Available from URL: http://www.promedcs.eu/sites/default/files/abstractbook_2016.pdf

DIAGNOSTIC AND THERAPEUTIC POSSIBILITIES IN PRIMARY SCLEROSING CHOLANGITIS

Pavel DRASTICH

Hepatogastroenterology, Institute for Clinical and Experimental Medicine, Prague; Czech Republic

Primary sclerosing cholangitis (PSC) is a chronic, progressive cholestatic liver disease of unknown origin. Male sex predominance in the third or fourth decades of life appears to exist with PSC. PSC is closely associated with inflammatory bowel disease (IBD), mainly ulcerative colitis (UC) in seventy to eighty percent of patients. PSC may precede the onset of UC or may develop following proctocolectomy. Conversely, 2.5–7.5% of patients with IBD develop PSC. PSC presents a significantly increased risk of hepatobiliary and colorectal neoplastic changes. The mechanisms responsible for the development of PSC are unknown.

The diagnosis of PSC is based on endoscopic retrograde cholangiopancreatography (ERCP) as a gold standard, but magnetic resonance cholangiopancreatography (MRCP) is rapidly developing as the preferred noninvasive method. ERCP or MRCP findings include multiple strictures and dilations of the intrahepatic and extrahepatic biliary ducts. Histological evaluation is not always necessary, but in small duct PSC it is mandatory for proper diagnosis. Transhepatic cholangiography is performed when ERCP is unsuccessful. The differential diagnosis of PSC includes congenital diseases (e.g., Caroli disease, choledochal cysts), secondary cholangiopathy, as observed in patients with collagen vascular diseases and in those with infiltrative and autoimmune diseases (e.g., eosinophilic cholangitis, histiocytosis X, sarcoidosis, IgG4-related sclerosing cholangitis). Infectious causes from any origin can cause multifocal liver abscesses that lead to a PSC-like appearance of the bile duct.

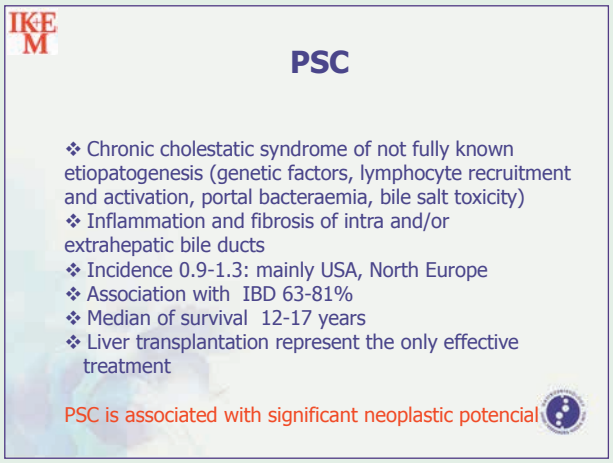
No effective medical therapy is available and liver transplantation (OLTx) is the only curative option how to improve survival currently available. Ursodeoxycholic acid (UDCA) is the most frequently prescribed drug in PSC. Low-dose UDCA (10–15 mg/kg/day) demonstrated efficacy in histological score and liver biochemistry, but did not show any beneficial effect on time to transplantation. On the other hand study using high-dose UDCA (up to 30 mg/kg/day) was prematurely terminated due to high occurrence of complications including increased risk of progression to liver transplantation and high risk varices. Currently, the role of UDCA in management of PSC patients is still not clear, but a high-dose UDCA (≥ 25 mg/kg/day) is contraindicated. Recent meta-analysis with PSC–IBD patients concluded, that UDCA may reduce the risk of advanced colorectal neoplasia or all colorectal neoplasia at doses of 8–15 mg/kg/day. But the chemoprotective effect of UDCA on colorectal neoplasia should be confirmed in further studies.

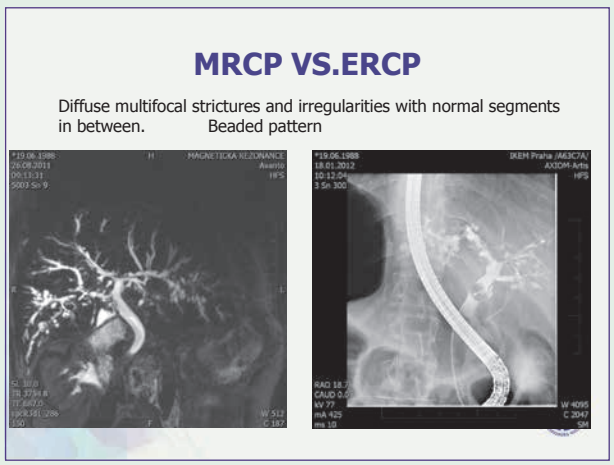
Up to 55% of patients with PSC will develop dominant bile duct strictures requiring balloon dilatation and short term stent placement through ERCP. Repeated endoscopic therapy is safe and helps preserve functioning of the liver parenchyma and improving transplant free survival. It is crucial and challenging to distinguish a dominant PSC stricture from cholangiocarcinoma, which is the cause of death in about 10–15% of PSC patients. Biliary tissue acquisition can be achieved by brush cytology and/or intraductal biopsy. Advanced techniques in cytology are nowadays using in clinical practice such as digital image analysis (DIA) and fluorescence in situ hybridization (FISH) that enhance the sensitivity and improves diagnostic

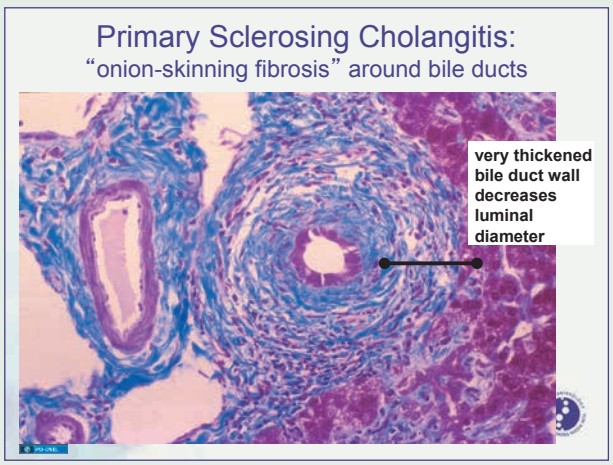
yield of brush cytology. Nonetheless early detection of cholangiocarcinoma in PSC remains a clinical challenge requiring a specialized diagnostic workup. PSC patients undergoing ERCP are routinely given antibiotics for prophylaxis of cholangitis.

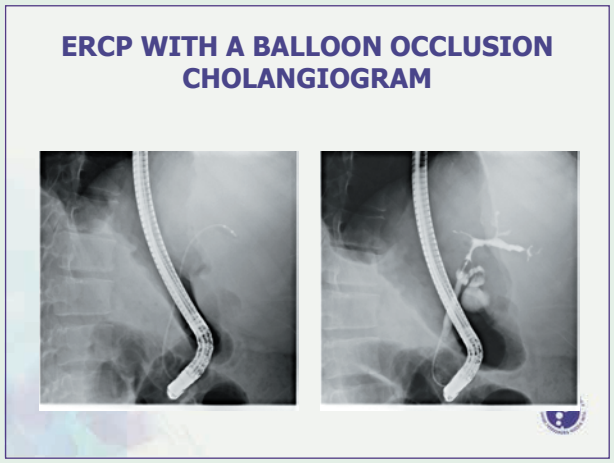
The outcome for patients with PSC who have undergone OLTx is excellent. PSC frequently recurs in the hepatic allograft (up to 20%) but retransplantation is seldom necessary. The course of UC after OLTx for PSC is frequently active despite immunosuppressive treatment.

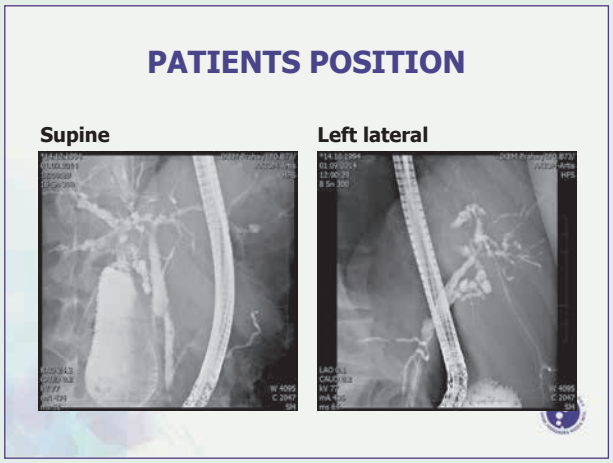
Drastich P. Diagnostic and therapeutic possibilities in primary sclerosing cholangitis. In: *11th International Symposium of Gastroenterology, Saint Petersburg, Russia, 12–14 May 2016*. [online].
Available from URL: http://www.promedcs.eu/sites/default/files/abstractbook_2016.pdf



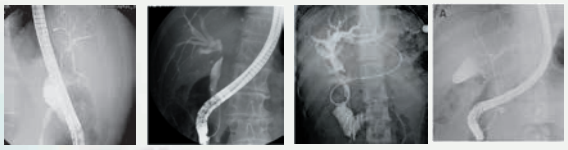








DIFFERENCIAL DIAGNOSIS



IgG 4 SC	Cholangiocel. Ca	Portal biliopathy	Biliary sarcoidosis
IgG 4 in serum in biopsy in bile?	Cytology, CA 19-9 Prot. biomarkers in bile?	Advanced PH	p-ANCA-, ACE+

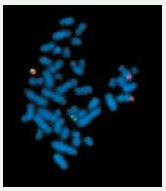
PSC VS. IAC

	PSC	IAC
Gender (M:F)	1.5:1	7:1
Age of onset	< 40 years	> 50 years
Presentation	Cholestatic liver enzymes	Obstructive jaundice
Cholangiogram	Beading, band-like strictures, peripheral pruning	Long smooth strictures, low CBD strictures
Cholangioscopy	Scarring, pseudodivertikula	Dilated and tortuous vessels
Raised serum IgG4 levels	< 20%	> 70%
Pancreatic involvement	< 5%	> 80%
Cholangiocarcinoma	9%	rarely
Association with IBD	80%	< 10%
Response to steroids	Rare (IgG4 + ve PSC)	97%

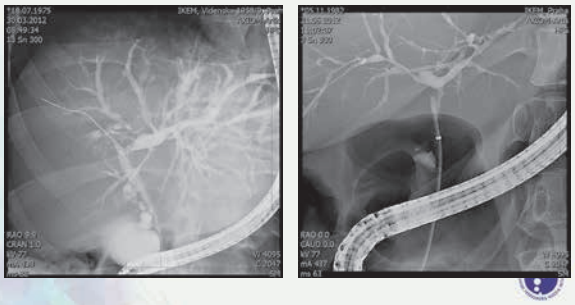
Nayagam JS et al. WJG 2016

CCC: MOST IMPORTANT DIF. DG IN DS

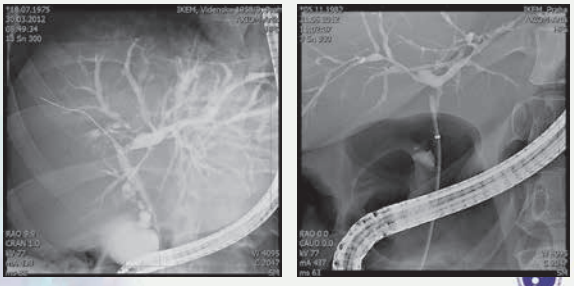
- Risk od CCC in PSC 10-15%
- Duration of PSC is not associated with increasing risk of CCC
- Diferential diagnosis of DS: PSC x CCC
- Brush cytology : specificity 100%, sensitivity 18-40%
  FISH (Fluorescence in situ hybridization) senzitivity 51-68%
- SpyGlass (Rey JW et al 2014) : targeted biopsies
- Protein biomarkers in bile:
  myeloperoxidase, complement C3, apolipoprotein B-100, kininogen-1 etc. (Navaneethan U et al 2014)
- CA 19-9



CCC YES OR NO??



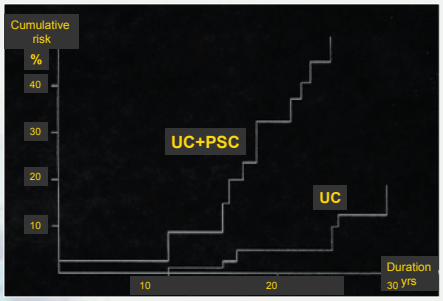
CCC YES OR NO??



YES NO

PSC a CRC

Cumulative risk of CRC



Adapted from Broomè, 1995

ENDOSCOPIC TREATMENT

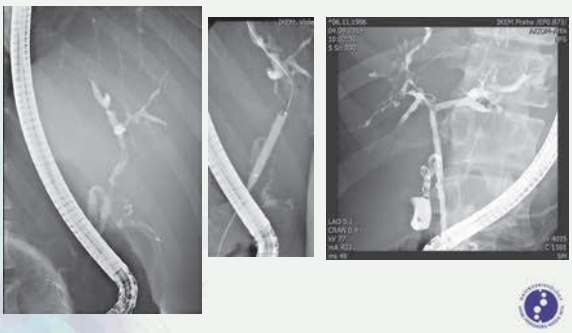
DOMINANT STRICTURE (DS)

- **Definition:** stricture with diameter < 1.5 mm in the CBD or < 1 mm in the hepatic duct
- Follow-up study of 9.8 years a new DS was found in 63% of pts Chapman MH et al 2012
- Obstructive symptoms and decompensation of liver function, risk of bacterial cholangoitis
- The mean survival rate of pts with DS is significantly less than those without. Chapman MH et al 2012

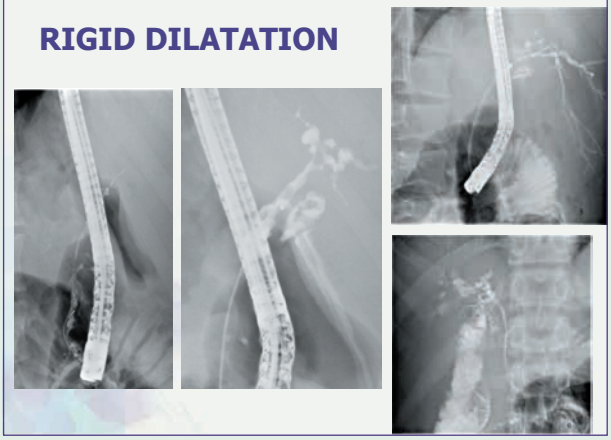
DILATATION

- **Gold standard:** repeated ballon dilatation +/- stent insertion for 1-2 weeks in case of cholangoitis and significant cholestasis, 500 dilatation in 96 pts (Gotthardt DN 2010 Heidelberg)
- **Ideal target:** dilatation up to 2 cm proximal of bifurcation on 18F (Stiehl A et al 2002), no consensus
- **Dilation procedure:** preferentially ballon dilatation, in case of failure, rigid dilatation 18-24F
- **Signs of success:** decrease of ALP≤ 1.5 of upper normal limits or at least ≥40%: improvement in survival rate and decreasing risk of CCC (Lindstrom L 2013, Al Mamari S 2013)

BALLON DILATATION



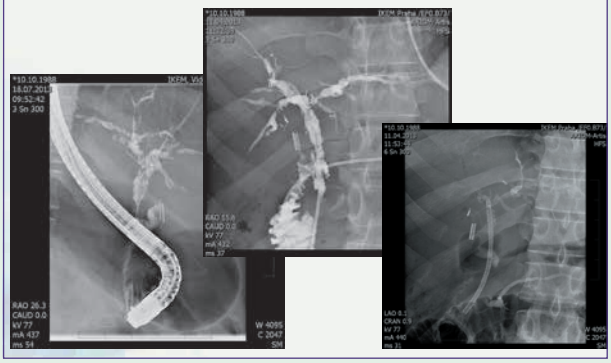
RIGID DILATATION



STENT INSERTION

- Stent insertion is usually succesfull based on small-size studies (Grijm R et al 1986)
- Short-term stent insertion is effective for 1-2 weeks (Ponsioen CY et al 1999; Van Milligen de Wit AW et al 1997)
- 1/3 of pts will underwent next ERCP as a urgent procedure (obstruction, cholangitis) due to stent obstruction by inflammatory cells and debris
- Stents are asscociated with increased risk of bacteriobilia (Rerknimitr R et al 2002)
- Stent insertion could be associated with obstruction of intrahepatic small ducts

PSC AND STENT



STENTS OR DILATATION?

Kaya M et al 2001

- Retrospective study
- 71 pt, 34 dilatation and rest combine therapy (endoscopy/PTD + stents)
- Improvement in cholestasis same in both groups
- Complications: higher in stent group (cholangitis, procedure-related complications)

European trial NCT01398917

- Prospective European randomised study
- Stent insertion (10F or 2x 7 F for 1-2 weeks) v.s. baloon dilatation 4-6 mm for 2 minutes)
- Planned number of pts:100
- Recruitment finished: 5/2015

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ATB IN PSC

- Positive bile cultures in 25% naive PSC patients scheduled for ERCP and 60% in those with previous ERCP (Bjornsson ES et al 2000)
  G- negative bacteria 25-40%
- ERCP could be associated with life-threatening cholangitis
- Rutine ATB prohylaxis in PSC patients before ERCP is essential!!!!

ENDOSCOPIC THERAPY AND SURVIVAL

Retrospective studies: transplant free survival

Study	3 –yrs survival without OLTx	4 –yrs survival without OLTx	5 –yrs survival without OLTx
Baluyut et al 2001			83 vs. 65% (p=0.027)
Gluck et al 2008	86.8vs. 76.3% (p=0.021)	82.8vs.76.3%, (p=0.021)	

DRUG TREATMENT FOR PSC

- Currently, there is no established drug treatment for PSC

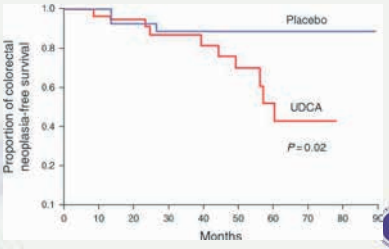
STUDIES WITH DIFFERENT DOSES OF UDCA IN PSC: IS THE EFFECT OF TREATMENT DOSE-DEPENDENT?

Author	Study design	Dose	Time	Results
Lindor** (1997)	double-blind	13 – 15 mg/kg bw/day	2 years	liver tests ++, histology 0, life expectancy improved by trend, (2nd evaluation of data 2009), UDCA well tolerated
Olsson (2005)	double-blind	17 – 23 mg/kg bw/day	5 years	life expectancy improved by trend, UDCA well tolerated
Mitchell** (2001)	double-blind	25 – 30 mg/kg bw/day	2 years	liver tests ++, histology +, life expectancy improved by trend, UDCA well tolerated
Lindor (2009)	double-blind	28 – 30 mg/kg bw/day	6 years	liver tests +, life expectancy not prolonged, severe side effects

+: improved; ++: markedly improved; 0: not improved

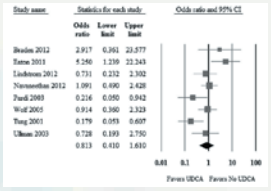
COLORECTAL NEOPLASIA – ROLE OF UDCA

- Long-term use of high-dose UDCA is associated with an increased risk of colorectal neoplasia in patients with UC and PSC

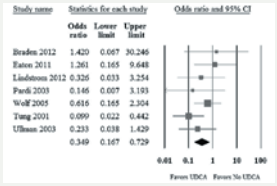


Eaton JE, et al. Am J Gastroenterol. 2011; 106:1638

UDCA AND RISK OF CRN: METANALYSIS



UDCA and risk of CRN

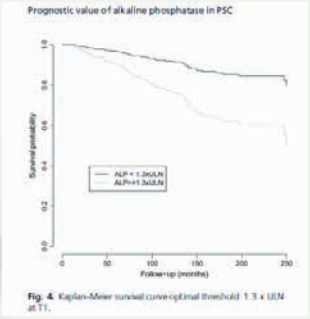


UDCA and risk of advanced CRN

Subgroup analysis: low-dose UDCA use (8-15mg/kg/d) was associated with significant risk reduction of CRN (OR, 0.19;95%CI,0.08-0.49)

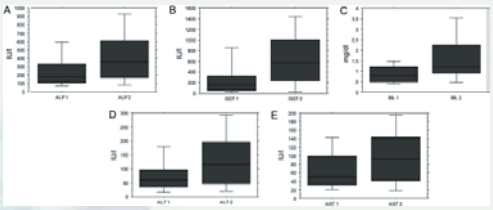
Singh S et al. Inflamm Bowel Dis 2013

ALKALINE PHOSPHATASE : A PROGNOSTIC VALUE



De Vries EMG et al. Liver international 2015

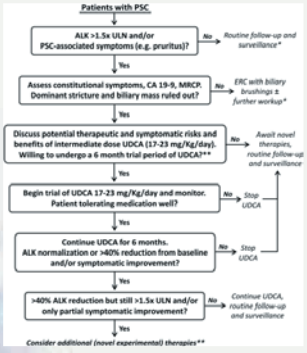
PROSPECTIVE EVALUATION OF UDCA WITHDRAWAL IN PATIENTS WITH PSC



Discontinuation of UDCA at 3 months

Wunsch E et al. Hepatology 2014

URSODEOXYCHOLIC ACID IN PSC: IF WITHDRAWAL IS BAD, THEN ADMINISTRATION IS GOOD (RIGHT?)



Tabibian JH et al. Hepatology 2014

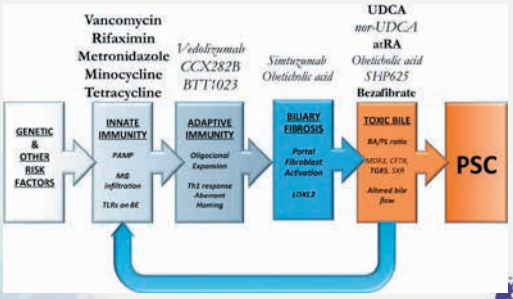
NOVEL THERAPY ON THE HORIZONT

norUDCA:

- protects cholangiocytes from luminal injury as hydrophilic bile acid (more hydrophilic than UDCA),
- which (in contrast to UDCA) is able to induce a bicarbonate-rich, less toxic bile since norUDCA (in contrast to UDCA) undergoes cholehepatic shunting.
- Additional mechanisms of nor UDCA include anti-fibrotic, anti-inflammatory and antiproliferative effects.

Halilbasic E et al. Dig. Dis. 2015

NOVEL THERAPIES ON THE HORIZONT



Williamson KD, Sem Liv Dis 2016

CONCLUSIONS

- Diagnosis of PSC is based on MRCP and ERCP, always in colaboration with colonoscopy. Liver biopsy is seldom needed.
- PSC – IBD represent a distinct phenotype of IBD
- The most important differential diagnosis is CCC and IAC
- Therapy of PSC is currently based mainly on dilatation of dominant stricture
- Currently, there is no established medical therapy
- Use of UDCA for PSC and as a chemopreventive agent for colorectal neoplasia should be carefully indicated and dosed properly
- Novel therapies on the horizont

ALCOHOLIC LIVER DISEASES: DIAGNOSTIC AND THERAPEUTIC POSSIBILITIES

Lubomir SKLADANY[1], Maria SZANTOVA[2], Michal BRUNCAK[1]

1. Hepatology, Gastroenterology and Liver Transplant Unit (HEGITO), Department of Internal Medicine II, F. D. Roosevelt University Hospital, Banska Bystrica. 2. Department of Internal Medicine 3, University Hospital, Bratislava; Slovakia

Background. The burden of liver disease in Europe is increasing – in contrast to most of other chronic diseases including cardiovascular; Slovakia (SK) ranks 4th in liver-related mortality in Europe (with decrease in life span by 1–2 decades), 6th in ALD-related premature deaths, and 9th in alcohol consumption. Alcoholic liver disease (ALD) is the most prevalent cause of advanced chronic liver disease (ACLD) in Europe. According to SK regional studies, ALD is responsible for at least 45% of liver cancers (HCC), transplantations and most of complications of ACLD – i.e. variceal bleeding, acute on chronic liver failure (ACLF), ascites etc. Alcohol, however, leads to 60 different diseases, some of them by proxy – i.e. violence, inflicted injuries and neonatal syndromes – and contributes 5.9% to global mortality and injuries.

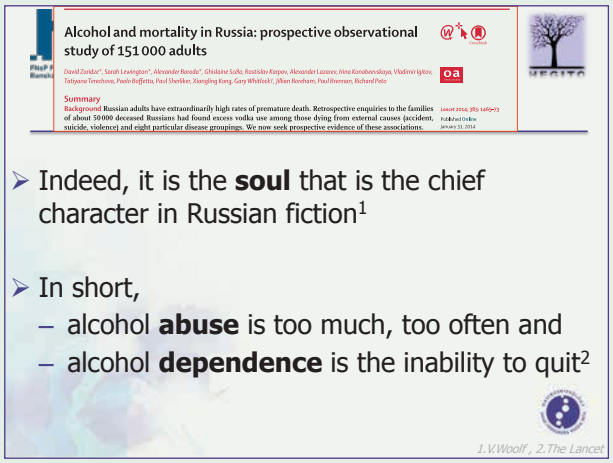
Diagnosis. There are at least four major ALD-related syndromes with clear-cut diagnostic criteria and significant mortality: *alcoholic hepatitis* (AH) with MDF, GAHS, Lille, ABIC and MELD diagnostic criteria with 1-month mortality of 30% in its severe form, *ACLF* (CLIF-OF; 20–80% 1-mo mortality according to degree), *withdrawal syndrome* (CIWA-Ar, DMS-5: delirium tremens; 5–15%), and specific *complications of ACLD* (MELD, Child-Pugh; two-thirds of ALD cirrhosis present with decompensated disease, 15% will develop hepatocellular carcinoma, survival rates at 5 years vary from zero to 80%, 60 to 90% of individuals die of their liver disease). AUDIT-C questionnaire of alcohol consumption given to 206 patients from 5 cities in SK, with median age of 57 years, 58% females, has shown 58% positivity of the test AUDIT-C1, and 21% and 31% positivity of AUDIT-C2 and C3 (risky drinking), respectively.

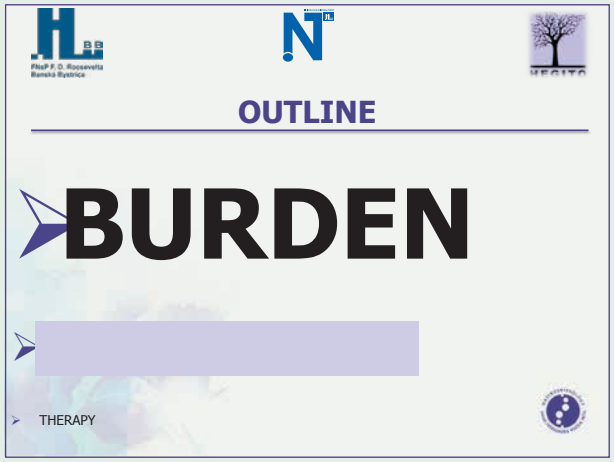
Therapy. The basis of management of any of ALD-related syndromes is guided abstinence. For 5.4×10^6 SK inhabitants there are 9 in- and 83 out-patient centres, respectively, with 1-y abstinence rates of under 20%. The uptake of specialized care in SK is very low (< 10%) due mainly to the lack of will to be treated – exact numbers are under investigation. Results of specific therapy for AH (corticosteroids and/or pentoxyphilline) are disappointing after STOPAH trial; in HEGITO retrospective study of 45 patients hospitalized with severe AH over 4 years (age 49, female 36%, MELD 27, steroids 82%), 1-mo mortality of responders was 11%, as compared to 50% in nonresponders ($p < 0,01$). Results in nonresponders direct the interest to liver transplantation and new trials. ACLF needs more investigation, promising seem growth factors and window of opportunity. In HEGITO study on ACLF, 1-mo mortality of grade 0–1 was zero as compared to 50% of gr. 2–3 ($p = 0.01$); CRP and WBC were predictors of ACLF ($p = 0.02$, and 0.06, respectively). To the best of our knowledge, there are no formal studies on withdrawal syndrome in SK. Most of complications of ACLD including HCC were scrutinized in HEGITO, their results are beyond the scope of this abstract and will be presented.

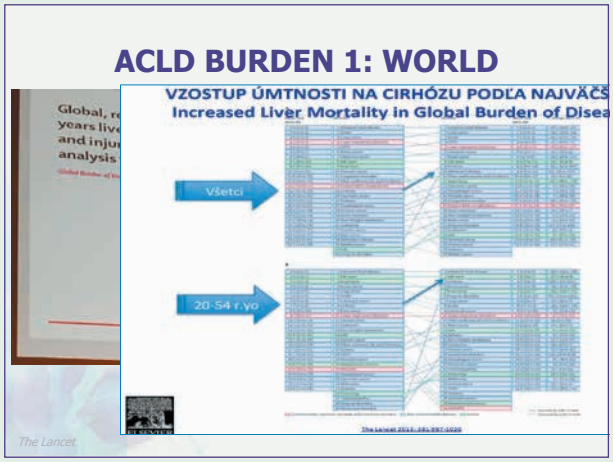
Conclusions. Liver related mortality is one of most important in Europe and SK. ALD is one of the most important causes of liver-related mortality in Europe and most important in SK. ALD has several forms with distinct diagnostic, prognostic and therapeutic algorithms. Their results support the notion that effective and efficacious therapy of ALD is one of unmet needs of current hepatology and public health medicine.

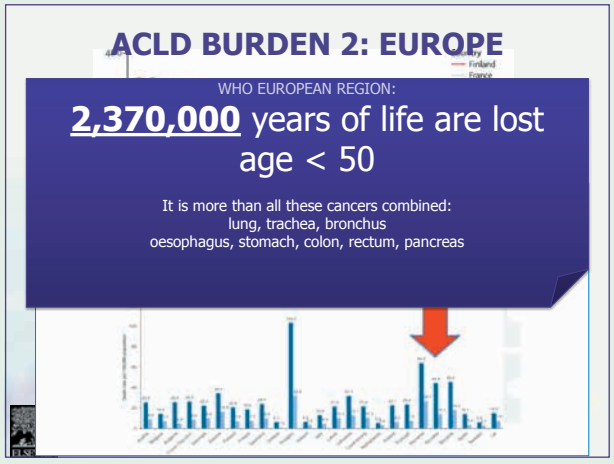
lubomir.skladany@gmail.com

Skladany L., *et al*. Alcoholic liver diseases: Diagnostic and therapeutic possibilities. In: *11th International Symposium of Gastroenterology, Saint Petersburg, Russia, 12–14 May 2016*. [online].
Available from URL: http://www.promedcs.eu/sites/default/files/abstractbook_2016.pdf





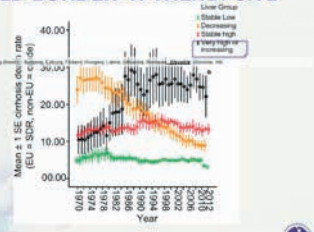


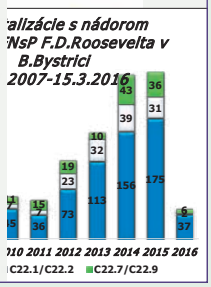


ACLD BURDEN 3: TREND/SK 1

World Health Organization regional office for Europe. European health for all database (HFA-DB). http://data.euro.who.int/hfadb/, 2014, ((accessed June 4, 2014)

ACLD BURDEN 4: TREND/ SK 2





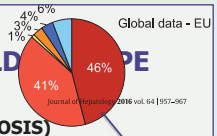
Journal of Hepatology 2016; 64: 957

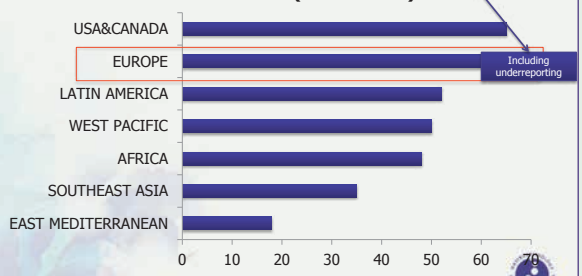
11th International Symposium of GASTROENTEROLOGY
12–14 May 2016, Saint Petersburg, Russia

WHAT PART OF LIVER-RELATED BURDEN IS ALCOHOLIC LIVER DISEASE (ALD)?

2.

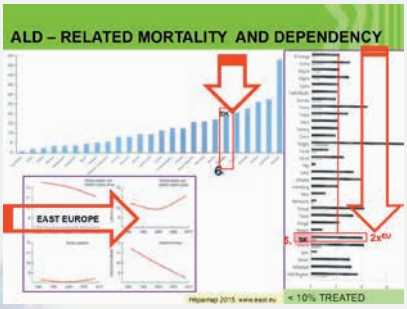
ALD BURDEN 1,2: WORLD ... PE





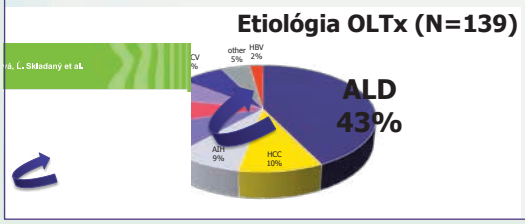
Stain E, submitted

ALD BURDEN 3: SK

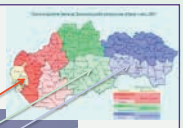


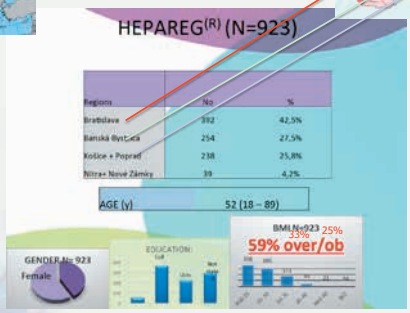
ALD BURDEN 3B: SK2 REGIONAL EXPERIENCE B.BYSTRICA

- ALD IS ETIOLOGY IN 40-80% OF COMPLICATIONS OF CIRRHOSIS IN REGION

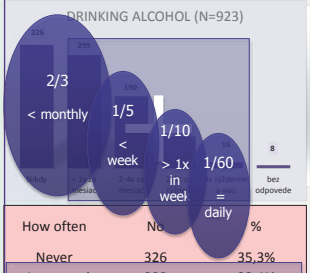


ALD BURDEN 3C: SK3



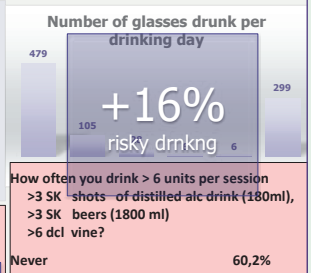


AUDIT C: HOW OFTEN, HOW MUCH X 2



How often	No	%
Never	326	35,3%
< 1x a month	299	32,4%
2-4x a month	190	20,6%
2-3x a week	84	9,1%
>= 4x a week	16	1,7%
No response	8	0,9%

63% = Complete AUDIT



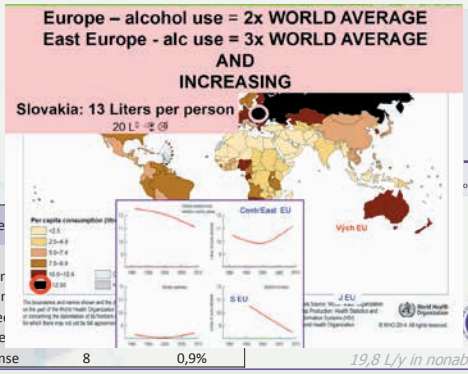
How often you drink > 6 units per session
>3 SK shots of distilled alc drink (180ml),
>3 SK beers (1800 ml)
>6 dcl vine?

Never	60,2%
< 1x in month	20,8%
Monthly	7,4%
Weekly	4,6%
Daily	0,9%
No response	6,2%

+34% risky drnkng

BUT ... VERY HARD TO BELIEVE IN THE LIGHT OF ...

Europe – alcohol use = 2x WORLD AVERAGE
East Europe - alc use = 3x WORLD AVERAGE
AND
INCREASING



How ofte	
Never	
< 1x a mor	
2-4x a mor	
2-3x a we	
>= 4x a we	
No response	8 0,9%

19,8 L/y in nonabstainers

11th Inter ASTROENTEROLOGY g, Russia

HELPLESS!

... YOUNG

BURDEN: ALCOHOL USE DISORDER

- ... ... **the most common mental disorders** [1]
- Applying (**DSM-5**)[2], in 2012–13
  - 36·0% of male and
  - 22·7% of female adults in the USA met the criteria for alcohol use disorders at some time in their lives, and
  - 17·6% of men and
  - 10·4% of women did so in the past year[3]
- AUD are **most prevalent in young** adulthood (age 18–29 years)[3]

1. Prevalence of and potential influencing factors for alcohol dependence in Europe. Eur Addict Res 2015; **21**: 109
2. Washington, DC: American Psychiatric Association, 2013
3. Grant. Results from the National Epidemiologic Survey on Alcohol and Related Conditions III. JAMA Psychiatry 2015; **72**: 757–66

X:

... POOR

ALD MORTALITY RELATES TO ... PRICE

Journal of Hepatology **2016** vol. 64 | 957–967

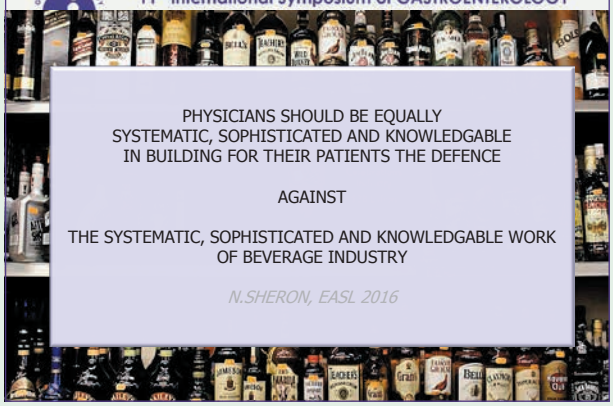
... UNEDUCATED (INCL.PHYSICIANS)

- Only 2-3% of publications on ALD *(Bataller, AASLD 2014)*
- Only 3% of resourcess to ALD research *(Bataller - CLIF april, 2016)*

UNEDUCATED LAY

Sheron, EASL 2016

11th International Symposium of GASTROENTEROLOGY



PHYSICIANS SHOULD BE EQUALLY
SYSTEMATIC, SOPHISTICATED AND KNOWLEDGABLE
IN BUILDING FOR THEIR PATIENTS THE DEFENCE

AGAINST

THE SYSTEMATIC, SOPHISTICATED AND KNOWLEDGABLE WORK
OF BEVERAGE INDUSTRY

N.SHERON, EASL 2016

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12–14 May 2016, Saint Petersburg, Russia

ALCOHOL BENEFIT HOAX

Alcohol use disorders

Jason P Connor, Paul S Haber, Wayne D Hall

Lancet 2016; 387: 988–98 Published Online

Alcohol use disorders are common in developed countries, where alcohol is cheap, readily available, and heavily promoted. Common, mild disorders often remit in young adulthood, but more severe disorders can become chronic

!

PHYSICIANS SHOULD BE VERY CAUTIOUS
IN
MAKING RECOMMENDATIONS / PUBLIC STATEMENTS
ABOUT POSITIVE EFFECTS OF ALCOHOL

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12–14 May 2016, Saint Petersburg, Russia

ALCOHOL: THE DIAGNOSIS

4.

HOW CAN ALC BECOME A PROBLEM IN HEPATOLOGY

- AAH
- ACLF
- ACLD = Ci
  - CiA
  - AKI
  - HRS
  - SBP
  - UGIB-V
- HCC

- Acute alcoholic hepatitis
- Acute over chronic liver failure
- Advanced chronic liver disease = Liver cirrhosis
  - Cirrhotic ascites
  - Acute kidney injury
  - Hepatorenal syndrome
  - Spontaneous bacterial peritonitis
  - Varicose bleeding
- Hepatocellular carcinoma

DIAGNOSTIC CRITERIA FOR ALD-RELATED SYNDROMES ARE WELL KNOWN

- AAH
- ACLF
- ACLD = Ci
  - CiA
  - AKI
  - HRS
  - SBP
  - UGIB-V
- HCC

- MADREY, MELD, LILLE (www…)
- CLIF-OF (www.)
- MELD (www.)
  - EASL guidelines 2010 (www.)
  - Angeli, J. Hepatol 2015
  - - " -
  - EASL Guidelines 2010 (www.)
  - Baveno VI, 2015
- EASL/EORTC Guidelines, 2012 (www.)

ALD IS UNDERDIAGNOSED

DG I S LATE

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WHAT CAN BE DONE?

APPLY AUDIT TO EVERYBODY

IN SK AND SIMILAR ALC RELATED COUNTRIES

WHY TO USE AUDIT - C

- **Physicians** often **overlook** alcohol problems in pts[1]
- Simply **asking patients** how much they drink often leads to an estimate **lower than the actual** number of alcoholic drinks per day
- Alcohol **disorders are treatable despite physician bias otherwise**[1]
- Without identification and treatment alcohol problems lead to significant morbidity and mortality:
- Alcohol is a major factor in suicides, homicides, violent crimes, and fatal motor vehicle accidents. Nearly 88,000 people die from alcohol-related causes annually, making it the third leading preventable cause of death in the United States[2]
- Alcohol is [illegible] secondarily implicated in a large number of
- [illegible] than the rate in matched controls[3]

1.Kitchens JM, 1994; 2.CDC, 2014; 3.Klatsky AL, 1992

Lancet 2014; 384(9958):1953

DG 2: KNOW THE POWER OF BIOMARKERS

	Monitor abstinence	Identify high-risk drinking	Time to normalise	Usefulness for detection of high-risk drinking	
				Sensitivity	Specificity
Routinely available tests					
Alcohol concentration in breath or blood	Yes	No	Hours	Low	High
γ-glutamyl transferase	No	Yes	4 weeks	Low	Moderate
Mean corpuscular volume of red blood cells	No	Yes	3 months	Low	Moderate
Aspartate aminotransferase	No	Yes	4 weeks	Low	Low
Tests done in specialised laboratories*					
Carbohydrate-deficient transferrin	No	Yes	4 weeks	Moderate	High
Ethyl glucuronide and ethyl sulphate	Yes	No	2 days	High	High
Phosphatidyl ethanol	No	Yes	4 weeks	High	High

*May be costly.

Table 2: Common biological markers

Lancet 2016; 387(10):1953

DG 2: IN ESTABILISHED LIVER DISEASE USE ADDITIONAL TOOLS

1. ALCOHOL USE: AUDIT complete
2. WITHDRAWAL RISK: CIWA-Ar
3. ALCOHOL RELATED PROBLEMS: APQ
4. ALCOHOL USE DISORDER: DSM-5
5. DEPENDENCE: LDQ
6. SEVERITY OF DEPENDENCE: SADQ
7. NEED FOR SPECIALIST CARE (incl. in-hospital)

DG 2: IN ESTABILISHED LIVER DISEASE USE ADDITIONAL TOOLS

1. ALCOHOL USE: AUDIT complete

WHAT TO DO WITH AUDIT RESULT?

RECALL POLICY

Patients scoring in the AUDIT 100

- **0–7**
  - should be given **basic alcohol education**,
- **8–15**
  - given **straightforward advice on reduction** of hazardous drinking,
- **16–19**
  - given straightforward advice in addition to brief counselling **and continued monitoring**,
- **20–40**
  - **referred for specialist** assessment

1. Connor, Lancet 2016

DG 2: IN ESTABILISHED LIVER DISEASE USE ADDITIONAL TOOLS

1. 1. ACUTE PHASE - WITHDRAWAL

   WITHDRAWAL RISK: CIWA

   The CIWA-Ar (commonly referred to as the CIWA)

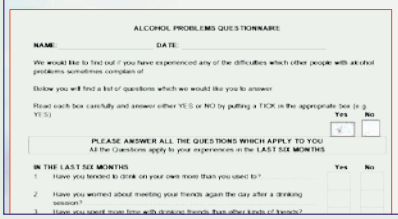
   with medications typically being administered at a score of 8-10 or higher.

   Sharaki MA. Recognition and management of withdrawal delirium (delirium tremens). N Engl J Med 2004; 371:2109-13.
2.
3.
4.
5.
6.
7.

N ENGL J MED 371;22 NEJM.ORG NOVEMBER 27, 2014

DG 2: IN ESTABILISHED LIVER DISEASE USE ADDITIONAL TOOLS

1.
2.
3. ALCOHOL RELATED PROBLEMS: APQ


ALCOHOL PROBLEMS QUESTIONNAIRE

NAME: DATE:

We would like to find out if you have experienced any of the difficulties which other people with alcohol problems sometimes complain of.

Below you will find a list of questions which we would like you to answer.

Read each box carefully and answer either YES or NO by putting a TICK in the appropriate box (e.g. YES)

PLEASE ANSWER ALL THE QUESTIONS WHICH APPLY TO YOU
All the Questions apply to your experiences in the LAST SIX MONTHS

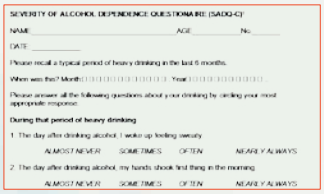
IN THE LAST SIX MONTHS	Yes	No
1 Have you tended to drink on your own more than you used to?		
2 Have you worried about meeting your friends again the day after a drinking session?		

DG 2: IN ESTABILISHED LIVER DISEASE USE ADDITIONAL TOOLS

1.
2.
3.
4. ALCOHOL USE DISORDER: DSM-5
5.
6.
7.

NIH National Institute on Alcohol Abuse and Alcoholism

DG 2: IN ESTABILISHED LIVER DISEASE USE ADDITIONAL TOOLS


SEVERITY OF ALCOHOL DEPENDENCE QUESTIONNAIRE (SADQ-C)

NAME AGE No.

DATE

Please recall a typical period of heavy drinking in the last 6 months.

When was this? Month Year

Please answer all the following questions about your drinking by circling your most appropriate response

During that period of heavy drinking

1. The day after drinking alcohol, I woke up feeling sweaty

ALMOST NEVER SOMETIMES OFTEN NEARLY ALWAYS

2. The day after drinking alcohol, my hands shook first thing in the morning

ALMOST NEVER SOMETIMES OFTEN NEARLY ALWAYS


Leeds Dependence Questionnaire - LDQ

Here are some questions about the importance of alcohol or other drugs in your life. Think about the main substance you have been using over the last 4 weeks and tick the closest answer to how you are yourself

Do you find yourself thinking about when you will next be able to have another drink or take more drugs?

Is drinking or taking drugs more important than anything else you might do during the day?

Do you feel that your need for drink or drugs is too strong to control?

5. DEPENDENCE: LDQ
6. SEVERITY OF DEPENDENCE: SADQ
7.

DG 2: IN ESTABILISHED LIVER DISEASE USE ADDITIONAL TOOLS

WHEN IS INPATIENT WITHDRAWAL INDICATED

Consider inpatient or residential assisted withdrawal **if** a service user **meets one or more** of the following criteria. They:

- Drink over **30 units** of alcohol per day
- Have a score of more than **30 on the SADQ**
- Have a history of **epilepsy**, or experience of withdrawal-related seizures or delirium tremens during previous assisted withdrawal programmes
- Need **concurrent withdrawal** from alcohol and benzodiazepines
- Regularly drink between 15 and 20 units of alcohol per day and have:
  - Significant psychiatric or physical comorbidities (for example, chronic severe depression, psychosis, malnutrition, congestive cardiac failure, unstable angina, chronic liver disease) **or**
  - A significant learning disability or cognitive impairment

7. NEED FOR SPECIALIST CARE (incl. in-hospital)

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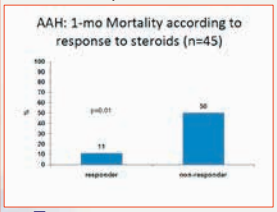
ALD: THERAPY

THERAPY OF ALD-RELATED SYNDROMES

- AAH
- ACLF
- ACLD = Ci
  - CiA
  - AKI
  - HRS
  - SBP
  - UGIB-V
- HCC

- Steroids, even > STOPAH *Thursz, NEJM,2015*



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- ...

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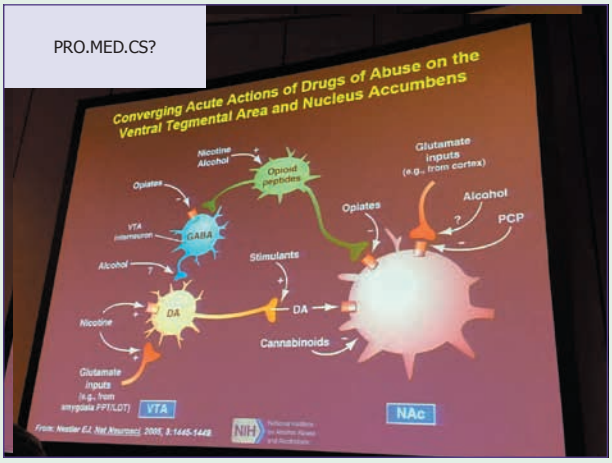
ALD: THERAPY IS ABSTINENCE

LONG-TERM ABSTINENCE
A)NON-PHARMACOLOGIC

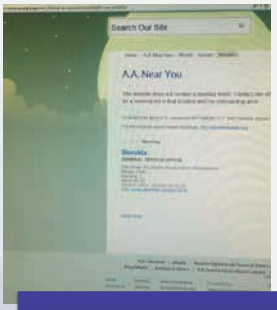
	Description	Level of evidence*
Cognitive behaviour therapy	This approach addresses cognitive, affective, and interpersonal triggers for alcohol use. It enhances drinking refusal self-efficacy[1] skills identifies and modifies alcohol-expectancies[2]; improves problem-solving skills; and develops more effective coping strategies, including relaxation approaches.	High[3–5]
Motivational enhancement therapy	This therapy is a patient-centred approach that enhances motivation to change behaviour. It uses a collaborative therapeutic approach to assist patients to recognise and resolve ambivalence, and develop their own reasons to reduce or abstain from drinking. Key strategies include collaborative identification of the gap between the patient's present and desired health (ie, goal-plan discrepancy), recognition of their resistance to change, avoidance of confrontational communication, and guided assessment of the pros and cons for change.	High[3–5]
Behavioural therapies based on conditioning	Cue-exposure: repeated exposure to conditioned cues (eg, image or smell of alcohol, or associated emotion) can induce habituation or craving. Exposure to cues during treatment in the absence of drinking (with or without coping skills practice) is thought to reduce habituation. It is often combined with other cognitive therapy or skills. Contingency management: this approach introduces a tangible reinforcer, such as money or vouchers, to increase session attendance or abstinence. It is more suitable for inpatient and residential settings, and needs more translatable evidence.	Low;[3] Moderate[6,7]
12-step facilitation	This approach offers continuous mutual peer support, usually in the form of self-help groups run by Alcoholics Anonymous. Participation is free of charge. Participants need to "surrender to a higher power" to facilitate change. Some groups use a buddy system (a sponsor) to provide support between group meetings.	Mixed[2,3,8,9]

*Summary based on authors' narrative review of the highest level of evidence for each treatment. †Individuals' beliefs about their ability to refrain from drinking. ‡Individuals' expectations about the effects of alcohol consumption.

PRO.MED.CS?



LONG-TERM ABSTINENCE
C)SELF-HELP

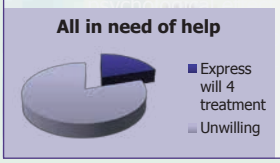


FIND YOUR LOCAL ALC ANONYMOUS CENTRE

LONG-TERM ABSTINENCE:
SELF – HELP NEEDED, BECAUSE:

LONG-TERM ABSTINENCE:
SELF – HELP NEEDED, BECAUSE:

1. O all alcohol-inflicted patients we identify (far) less than 50%
2. Of those identified allopathic medicine has proposal for only those who want to quit and express this will
   – Which is contraintuitive in the context of known



LONG-TERM ABSTINENCE:
SELF – HELP NEEDED, BECAUSE:

1. O a… ntify (far) less tha…
2. Of t… e has pro… quit and exp…
   – W… of known p… on-making
3. Of those willing allopathic medicine succeeds long-term in less than 10-20%

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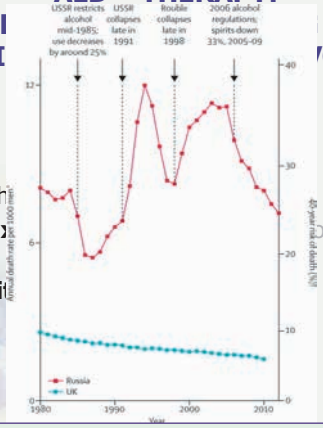
Med J Aust. 1992 Feb 3;156(3):212-5.
Why alcoholism is not a disease

WHY?

ALD – THERAPY:

EQUAL I… DRUGS, PHYSI… VOCATS

Drug Alcoh…
Alcohol **ta**… …ohol in Europe
Availabili…



CONCLUSIONS

1. Global health of CEE (SK) is heavily inflicted by alcohol
2. Sophistically targeted are young and desperate cohorts
3. Action on the side of physicians is limited by
   1. Attitude: Controversies as to disease vs decision
   2. Lack of effective interventions and drugs in hands of carers
   3. Lack of interdisciplinary networking (psychol, psychiatr, addictol, …)
4. Unless allopathic approaches (drugs, network) ensue, physicians should
   1. Stop being passive / fingerpointing towards alcoholics
   2. Make up their minds as to the essence of alcoholism, and – if
   3. Increasing the price (Taxing) an
   4. Decreasing availability of alcohol

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CONCLUSIONS

1. Global health of CEE (SK) is heavily inflicted by alcohol
2. Sophistically targeted are young and desperate cohorts
3. Action on the side of physicians is limited by
   1. Their ambivalent attitude to alcoholism: as to disease vs decision
   2. Lack of effective interventions and drugs
   3. Lack of interdisciplinary networking (psychol, psychiatr, addictol, …)
4. Unless allopathic approaches (drugs, network) ensue, physicians should
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   1. Attitude: Controversies as to disease vs decision
   2. Lack of effective interventions and drugs in hands of carers
   3. Lack of interdisciplinary networking (psychol, psychiatr, addictol, …)
4. Untill drugs, networks, etc. come to use, physicians should
   1. Stop being passive / fingerpointing towards alcoholics
   2. Stop being ambivalent as to the essence of alcoholism
   3. **Become advocates for**
      1. **Increasing the price (Taxing) an**
      2. **Decreasing availability of alcohol**

NON-ALCOHOLIC STEATOHEPATITIS (NASH): WHICH THERAPY DO WE HAVE?

Tomasz MACH

Department of Gastroenterology and Hepatology, Jagiellonian University Medical College, Krakow; Poland

Non-alcoholic steatohepatitis (NASH) is the progressive form of non-alcoholic fatty liver disease (NAFLD), which is the most common chronic liver disease in Western countries. NAFLD encompasses a wide spectrum of histologic lesions from simple steatosis to NASH, which can progress to advanced fibrosis, cirrhosis and hepatocellular carcinoma. NASH is strongly associated with obesity, insulin resistance (IR), type 2 diabetes mellitus, hypertension, dyslipidemia, and is regarded as the liver manifestation of the metabolic syndrome, with a close relation to cardiovascular disease. The pathogenesis is not fully elucidated, but are considered: sedentary lifestyle, unproper diet, genetic predisposition, IR, oxidative stress, cytokine and adipokine dysregulation, immune mediated events, the gut microbiome and altered intestinal permeability. Main targets of intervention are: treatment of metabolic syndrome components and treatment oriented on pathogenetic factors. First-line therapy involves: lifestyle modifications, regular exercise, dietary changes (caloric restriction, diet high in monounsaturated fatty acids, omega-3 fatty acids, and low in fructose, e.g., Mediterranean diet). Pharmacotherapy in patients with biopsy-proven NASH includes:

1) Antidiabetics/insulin sensitizer agents, e.g. pioglitazone (PIVENS trial, meta-analysis – drug improves liver histology and fibrosis, several adverse effects), metformin (not recommended by EASL, useful in type 2 diabetes mellitus), glucagon-like peptide-1 agonists.
2) Ursodeoxycholic acid (UDCA; immunomodulatory, antiinflammatory, antiapoptotic, antioxidant, antifibrotic properties) improves IR, ALT and histologic lesions in high doses, modulates lipid metabolism (Ratziu V., *et al*. J Hepatol 2011).
3) Lipid-lowering agents: statins (e.g. atorvastatin).
4) Antioxidants – vitamin E 800 IU/day in non-diabetic adults (PIVENS trial, improves histology), pentoxiphylline.
5) Obeticholic acid (activates the farnesoid X nuclear receptor; FLINT trial, improves liver histology and fibrosis, but several adverse effects).
6) Gut microbiota modulators and many drug candidates targeting different metabolic pathways are currently studied in clinical trials.

Where do we stand with regard to NASH therapy? The majority of agents have either mild efficacy on liver and cardiovascular-related outcomes or requires further and larger studies in order to validate the current findings and to establish the long-term safety in NASH before establishing definitive recommendations. Many clinical trials are ongoing with hope to find the effective medications in NASH.

Mach T. Non-alcoholic steatohepatitis (NASH): Which therapy do we have? In: *11th International Symposium of Gastroenterology, Saint Petersburg, Russia, 12–14 May 2016*. [online].
Available from URL: http://www.promedcs.eu/sites/default/files/abstractbook_2016.pdf

SCREENING OF COLORECTAL CARCINOMA: HOT TOPICS IN CURRENT CLINICAL GASTROENTEROLOGY

Tomas GREGA, Stepan SUCHANEK, Miroslav ZAVORAL

Department of Internal Medicine, First Faculty of Medicine of Charles University and Military University Hospital, Prague; Czech Republic

Colorectal cancer (CRC) is the second most common cause of death from malignancy in the world, with 1.2 million new cases and 640 000 deaths yearly. Colonoscopy remains the gold standard method for colorectal cancer screening, however the compliance is less than 50%. One of the most important barriers to screening is a lack of perceived risk of colorectal cancer among average-risk patients and primary care providers. The possibility of influencing the participation rate for CRC screening include shift of opportunistic individual testing to organized population screening. Another screening barrier represents the fear of people from invasive examinations. Several non-invasive screening tests are available, and various professional organizations have different recommendations on which screening test to use. In the Czech Republic, the organized non-population-based National Colorectal Cancer (CRC) Screening Program has been running since year 2000. Program is focused on asymptomatic individuals with average risk of CRC. In 2014, the transition to population-based program was realized by personalized mail invitations of program non-participants. It resulted in the improvement of target population coverage by 4.6% per year followed by increasing colorectal neoplasia detection (42% for adenomas and 20% for cancers). Future directions of CRC screening can be seen in determining the optimal screening methods that are less invasive, with high sensitivity and accepted by the general population. One such tool can be an immunochemical test for occult blood in the stool (FIT). FIT screening is associated with a higher population uptake than guaiac FOBT screening and has higher sensitivity for detecting of advanced neoplasia. On the other hand, there are few limitations. Firstly, the results of the test depend on the environmental temperature and the sample-return time. Another disadvantage is the lack of standardization of haemoglobin concentrations among different FIT tests. Very attractive screening method remains the DNA testing in stool or serum. Tests have a higher sensitivity but lower specificity compared to FIT. Their using is limited by the complicated storage and high price. CT-colonography has the potential advantage of requiring limited bowel preparation and can detect 70–100% of the advanced neoplasias detected by colonoscopy. The field of colon imaging is rapidly evolving and aims to improve CRC screening by lowering the patient burden and enhancing neoplasia detection. One such alternative is to screen by colon-capsule endoscopy. Recently published Irish prospective study showed high sensitivity and specificity (89%, resp. 96%) in the detection of colorectal neoplasia and reduce the need for colonoscopy to 71%. Other possibilities for improving the effectiveness of screening CRC can be seen in the scoring of the likelihood of colorectal neoplasia in the target population. Kaminski *et al*. in Polish retrospective study identified risk factors associated with colorectal neoplasia. These were age, sex, family history of CRC, smoking and obesity. Combination of these changes can increase the preventive effect of CRC screening, which will lead to reduction of incidence and mortality of CRC.

References:

1. Jemal A., Bray F., Center M.M., Ferlay J., Ward E., Forman D. Gobal cancer statistics. CA Cancer J Clin. 2011; 61(2): 69–90.
2. Klabunde C.N., Vernon S.W., Nadel M.R., *et al*. Barriers to colorectal cancer screening: a comparison of reports from primary care physicians and average-risk adults. Med Care 2005; 43: 939–944.
3. Holleran G., Leen R., O'Morain C., *et al*. Colon capsule endoscopy as possible filter test for colonoscopy selection in a screening population with positive fecal immunology. Endoscopy. 2014 Jun; 46(6): 473–478.
4. Kaminski M.F., Polkowski M., Kraszewska E., *et al*. A score to estimate the likelihood of detecting advanced colorectal neoplasia at colonoscopy. Gut. 2014 Jul; 63(7): 1112–1119.
5. Kuipers E.J., Rösch T., Bretthauer M. Colorectal cancer screening-optimizing current strategies and new directions. Nat Rev Clin Oncol. 2013 Mar; 10(3): 130–142. doi: 10.1038/nrclinonc.2013.12. Epub 2013 Feb 5. Review. PubMed PMID: 23381005.

Zavoral M., *et al*. Screening of colorectal carcinoma: Hot topics in current clinical gastroenterology. In: *11th International Symposium of Gastroenterology, Saint Petersburg, Russia, 12–14 May 2016*. [online].
Available from URL: http://www.promedcs.eu/sites/default/files/abstractbook_2016.pdf

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SCREENING OF COLORECTAL CARCINOMA: HOT TOPICS IN CURRENT CLINICAL GASTROENTEROLOGY

Tomas GREGA, Stepan SUCHANEK, Miroslav ZAVORAL

Department of Internal Medicine, First Faculty of Medicine of Charles University and Military University Hospital, Prague
CZECH REPUBLIC

EPIDEMIOLOGY

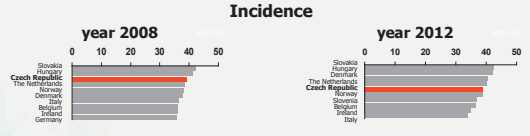
COLORECTAL CANCER (CRC)

- 2nd most common cancer in women and 3rd most common cancer in men worldwide
- 1.2 million new cases, 640 000 deaths per year
- 2.6–5.6% of advanced adenomas annually progress to invasive CRC
- high incidence remains in some parts of the world
  - middle and eastern Europe, Asia and South America

Kuipers E.J., et al. Nat. Rev. Clin. Oncol 2013.

Epidemiology in Europe

Incidence

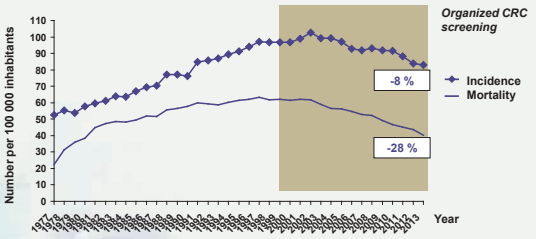


Mortality

	Year 2008		Year 2012	
Czech Republic	No. of patients	position in Europe	No. of patients	position in Europe
Incidence	7.771	3.	8.336	5.
Mortality	3.915	3.	3.628	9.

Ferlay J., et al. Globocan 2012, http://globocan.iarc.fr (published in 2013).

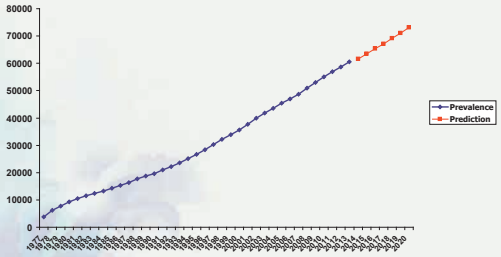
EPIDEMIOLOGY IN THE CZECH REPUBLIC



- compared the period 1995–1999 (before organized screening program) and 2009–2013 (actual data)
  - incidence: decrease of 8%
  - mortality: decrease of 28%

Source: National Oncologic Register of Czech Republic.

Prevalence of CRC in the Czech Republic



Source: National Oncologic Register of Czech Republic.

SCREENING

CRC SCREENING

- effective tool of secondary prevention
- detect sporadic CRC (80–90% of all CRC cases)
- focuses on asymptomatic individuals
  - ≥ 50 years of age
  - with negative family or case history of CRC
  - without chronic inflammatory bowel disease
- multiple screening options available

SCREENING METHODS

- Stool-based tests
  - guaiac-based fecal occult blood test (gFOBT)
  - immunochemical test (FIT)
  - fecal DNA testing
- Endoscopic examinations
  - colonoscopy / flexible sigmoidoscopy
  - capsule colonoscopy
- Radiologic examinations
  - CT colonography

EFFECT OF SCREENING METHODS

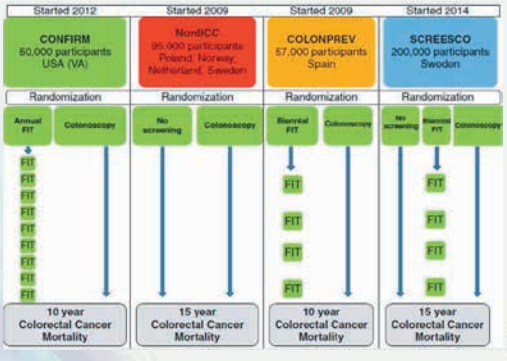
- main aim: decrease of mortality and incidence

	incidence	mortality	trial
gFOBT	↓ 18–20%	↓ 22–32%	USA – Minnesota (every 2/every 1 year)
Flex Sig	↓ 23%	↓ 31%	UK Flex Sig trial
Colonoscopy	-	↓ 60%	USA – Medicare – not randomized

- main problem:
  - missing RCT of effectiveness of colonoscopy

European Guidelines for CRC screening and diagnosis, 2010.
Zauber A.G., et al. Dig Dis Sci 2015.

COLONOSCOPY AND EFFECTIVENESS



Robertson DJ, et al. Gut 2015

ORGANIZED SCREENING PROGRAM

ORGANIZED SCREENING PROGRAMS

- requiring public responsibility by law
- supervision by national team

- opportunistic screening program
  - screening initiative is up to the individual and to motivated providers
- population-based screening program
  - target individuals are personally invited

Zavoral M., et al. WJG 2009.

EUROPEAN RECOMMENDATION

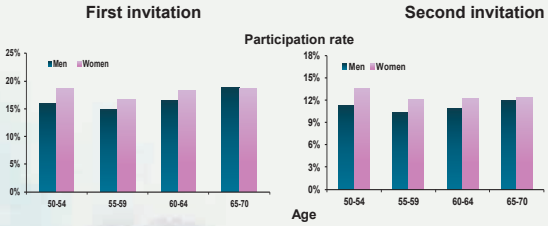
- organized screening programs (population – based)
- determination of screening intervals
- quality indicators of CRC screening programs
  - early impact indicators
    - coverage of target population (min. 45–65%)
    - detection rate of adenoma and carcinoma
  - long impact indicators
    - incidence and mortality of CRC

European guidelines for quality assurance in CRC screening and diagnosis, 2010.

NATIONAL CRC SCREENING PROGRAM IN THE CZECH REPUBLIC

- years 2000–2014
  - organized opportunistic screening program
- since 2014
  - address invitation to screening program
  - population-based screening program
- age 50–54 years:
  - FIT annually → positivity → FIT + colonoscopy
- age ≥ 55 years:
  - FIT biannually / screening colonoscopy

Population-based CRC screening



- First invitation:
  - 1.5 million persons (53% of target population)
  - participation 17.3%
- Second invitation:
  - 100,000 re-invited
  - participation 11.8%

Source: Institute of biostatistic and analysis, Masaryk University Brno.

FOBT AND PREVENTIVE COLONOSCOPIES (2013–2014)

- increase of FOBT by 30%
- increase of screening colonoscopies by 85%

Screening examination	Year 2013	Year 2014	2013 vs. 2014
FOBT	574 108	744 015	+30%
Total number of preventive colonoscopies	236 016	263 060	+11%
FOBT + colonoscopy	17 499	23 365	+34%
screening colonoscopy	4 999	9 236	+85%

Source: Institute of biostatistic and analysis, Masaryk University Brno.

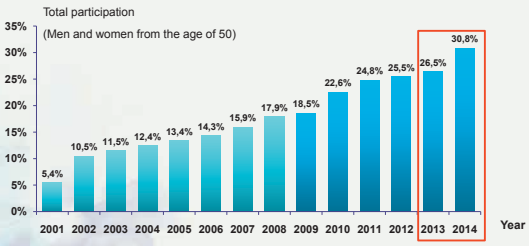
DETECTION OF COLORECTAL NEOPLASIA

- higher detection of adenomas by 42%
- higher detection of carcinomas by 20%

	Year	Colonoscopy	Adenomas	Carcinomas
FOBT + colonoscopies	2013	21,972	8,758	818
	2014	28,795	11,779	959
Screening colonoscopies	2013	4,966	1,361	49
	2014	9,288	2,613	81
Total number of preventive colonoscopies	2013	26,938	10,119	867
	2014	38,023	14,392	1,040

Source: Institute of biostatistic and analysis, Masaryk University Brno.

TOTAL COVERAGE OF TARGET POPULATION



- annual increase (2013 → 2014): **4.3 %**

Source: Institute of biostatistic and analysis, Masaryk University Brno.

BARRIERS TO CRC SCREENING

- low perception of CRC risk in average asymptomatic population
- fear of invasive examinations
- low education status
- lower levels of income

Knight J.R., et al. Prev Chronic Dis 2015.

HOW TO INCREASE PARTICIPATION IN THE SCREENING

- health education programs to the general public and to health professionals to increase awareness about CRC prevention
- noninvasive and cost/benefit screening examinations
- select subjects at higher than average risk of developing sporadic CRC

HOT ISSUES IN CRC SCREENING

QUANTITATIVE IMMUNOCHEMICAL FOBT – OPTIMAL CUT OFF

- different sensitivity – cut-off limits
- concentration of fecal hemoglobin
  - varies by age and sex
- results depend on the environmental temperature and the sample-return time
- optimal cut-off value: 75–100 ng/mL

Nakama H., et al. Eur J Cancer 2001; Goede S.L., et al. Gut 2013.

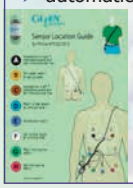
FECAL DNA TESTING

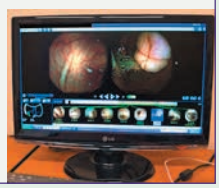
- Multitarget – evaluate multiple markers
  - methylated promoter regions of genes BMP3 and NDRG4
  - KRAS and β-actin mutations
  - presence of human hemoglobin
- higher sensitivity
  - 92.3% vs. 73.8% FIT
- lower specificity
  - 86.6% vs. 94.9% FIT
- limitations:
  - complicated storage
  - high price

Imperiale T. F, et al. N Engl J Med. 2014.

CAPSULE COLONOSCOPY (CC) PILLCAM COLON 2

- size 11.6 × 31.5 mm
- angle of vision 172° (instead 156°)
  - cover almost 360° of colon
- adaptive frame rate (AFR)
  - 4–35 frames per second
- automatic detection of small bowel





CAPSULE COLONOSCOPY – EXPERIENCE IN THE CZECH REPUBLIC

- multicentric prospective study (2011–2014), 175 patients
- high specificity and sensitivity in detection of colorectal neoplasias in screening population
- adequate screening option

	Colonoscopy		Capsule colonoscopy					
	Prevalence number, proportion		Sensitivity matching results, proportion among OC+, CI			Specificity matching results, proportion among OC-, CI		
Polyp	121	**51%**	98	**81%**	CI 73-88%	100	**87%**	CI 79-93%
≥ 6 mm	39	**17%**	30	**77%**	CI 61-89%	192	**97%**	CI 94-99%
≥ 10 mm	16	**7%**	14	**88%**	CI 62-98%	217	**99%**	CI 96-100%
Adenoma	63	**27%**	51	**81%**	CI 69-90%			
≥ 10 mm	11	**5%**	11	**100%**	CI 72-100%			
Carcinoma	2	**1%**	2	**100%**		234	**100%**	CI 94-99%

Zavoral M. Gastroent hepatol 2014.

CONCLUSIONS

- CRC screening is associated with decreased CRC incidence and mortality
- The effectiveness of CRC screening depends on adequate participation of the target population
- Opportunistic testing is shifting to organized population screening with monitoring and assurance of quality indicators
- Options for screening depend upon the healthcare infrastructure of the country including the availability of endoscopic resources

HEREDITARY POLYPOSIS SYNDROME. WHAT HAVE WE LEARNED IN THE LAST TEN YEARS?

Martin HUORKA

V. Intern clinic, Department of Gastroenterology and Hepatology, V. Intern clinic Faculty of Medicine, University Comenius, Bratislava-Ruzinov; Slovakia

Although intestinal polyposis syndromes are relatively rare, awareness of the existing health risks is important for patients and their families affected by these disorders. Intestinal polyposis syndromes can be divided, based on histology, into the broad categories of familial adenomatous polyposis (FAP) and hamartomatous polyposis syndromes.

Several genetic disorders may present with GI polyps. FAP is the most common inherited polyposis syndrome, encompassing multiple phenotypes. These phenotypes range from a mild phenotype in attenuated polyposis syndrome to specific clinical syndromes recognized many decades prior to the discovery of the adenomatous polyposis (APC) gene.

More recently described syndromes MUTYH-Associated Polyposis, Hereditary Mixed Polyposis Syndrome, Serrated Polyposis Syndrome, and Polymerase Proofreading Associated Polyposis. These new type of polyposis syndrome has been defined and is associated with various types of serrated polyps.

– *MUTYH-associated polyposis* (MAP) was originally identified in Welsh kindred in 2002 and is an autosomal recessive (unlike most other polyposis syndromes) adenomatous polyposis syndrome most commonly with an attenuated FAP-like phenotype.

– *Hereditary mixed polyposis syndrome* (HMPS) is characterized by the presence of polyps of several different types and/or individual polyps that are composed of more than one histologic type. The syndrome appears to be inherited as an autosomal dominant trait. The polyps are confined to the colon, are between 1–15 in number (and rarely exceed 50), and may resemble adenomas macroscopically.

– *Serrated polyposis syndrome* (SPS; formerly known as hyperplastic polyposis syndrome) is a rare, likely hereditary, polyposis syndrome most common in those of northern European ancestry. It is also more common among current smokers.

– *Polymerase proofreading associated polyposis* (PPAP) is another autosomal dominantly inherited polyposis syndrome recently described with a variable phenotype that may include 10–100 adenomas, often presenting before 60-years, with or without colorectal carcinoma, and/or isolated early onset colorectal carcinoma.

The topic of hereditary polyposis syndromes is truly an evolving field with expansion in the molecular and phenotypic characterization of these syndromes. In the near future, the genetic mechanism(s) of sessile serrated polyposis may be unravelled and new syndromes or genetic mechanisms for familial colorectal carcinoma will be discovered.

Huorka M. Hereditary polyposis syndrome. What have we learned in the last ten years? In: *11th International Symposium of Gastroenterology, Saint Petersburg, Russia, 12–14 May 2016*. [online].
Available from URL: http://www.promedcs.eu/sites/default/files/abstractbook_2016.pdf

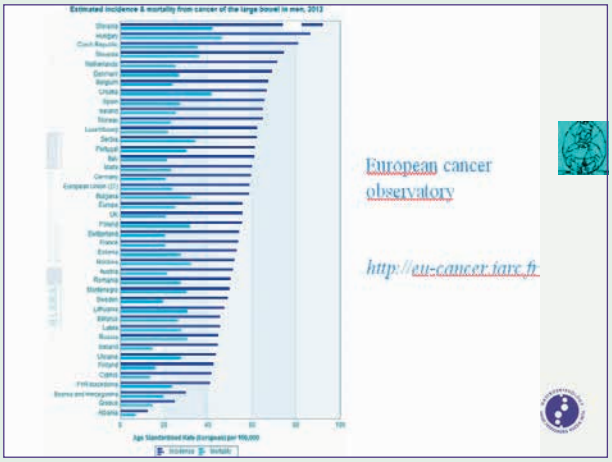
11th International Symposium of GASTROENTEROLOGY
12–14 May 2016, Saint Petersburg, Russia

HPS – HEREDITARY POLYPOSIS SYNDROME.

WHAT HAVE WE LEARNED IN THE LAST TEN YEARS?

Martin Huorka

Department of Gastroenterology and Hepatology
V. intern clinic Faculty of Medicine, University Comenius, Bratislava
SLOVAKIA



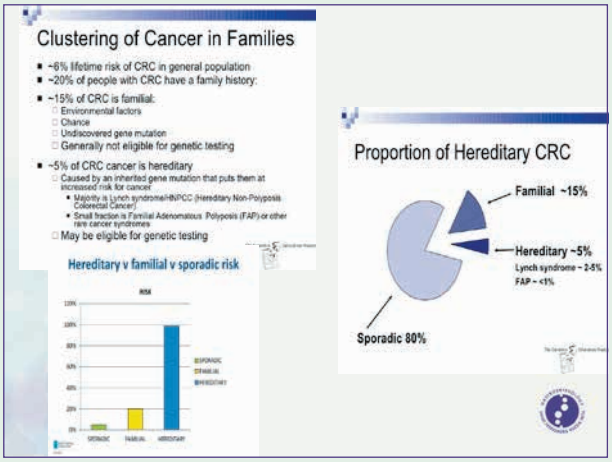
THE BASIC EPIDEMIOLOGICAL FACTS ABOUT COLORECTAL CANCER

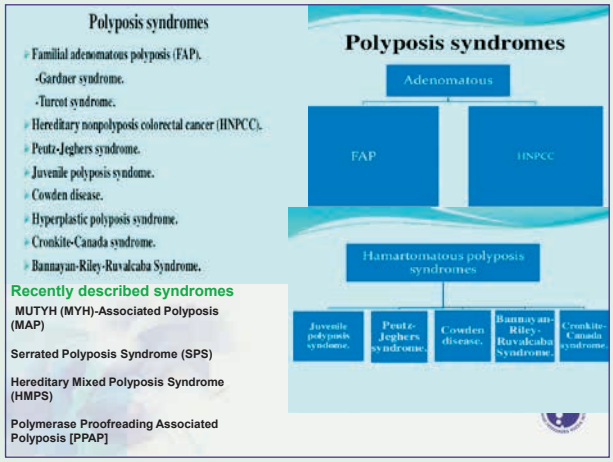
The Facts

- ~137,000 men and women per year diagnosed with colorectal cancer
- 5-year survival rate for early stage colorectal cancer is >90%
- 4 out of 10 cancers are found at an early stage
- Polyps are the precursor to colorectal cancer
- Only ½ of the people that are due for colon screening pursue screening!

Even Polyps Have Dreams
Dailymedicalexaminer.com

Cancer.org





Recently described syndromes

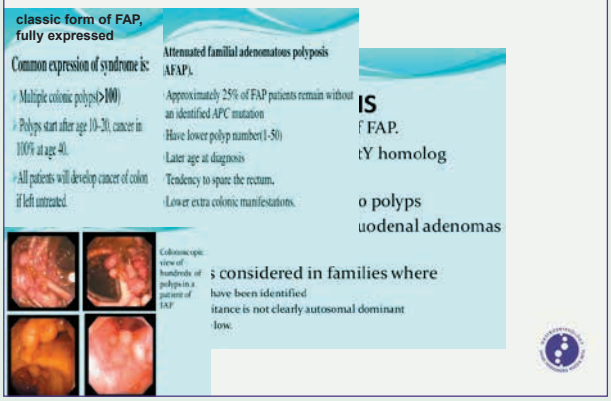
MUTYH (MYH)-Associated Polyposis (MAP)

Serrated Polyposis Syndrome (SPS)

Hereditary Mixed Polyposis Syndrome (HMPS)

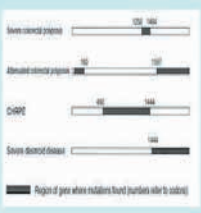
Polymerase Proofreading Associated Polyposis [PPAP]

FAP- GENETIC AND CLINICAL FEATURES, PHENOTYPES



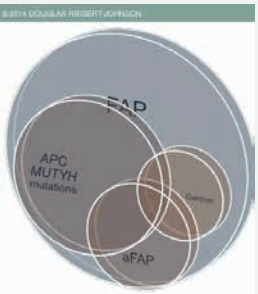
THE PRESENTATION AND SEVERITY OF FAP

- The presentation and severity of disease is related to the site of the *APC* gene mutation.
- Proximal *APC* mutations (proximal to codon 1249) produce a milder attenuated phenotype with sparse polyposis.
- *APC* mutations between codons 1250 and 1330 present with tremendous degrees of polyposis.



IS DG OF FAP CORRECT WITHOUT IDENTITY OF GENE MUTATIONS?

Some patients with FAP, attenuated (lesser FAP) and Gardner syndrome do not have *APC* or *MUTYH* mutations.



polyposis *POLE, POLD1*). Patients with aFAP have a 50% chance or less of having a detectable *APC* mutation.

Consequences of FAP

- Colorectal adenomatous polyps begin to appear at an average age of 16 years (range 7-36 years)
- Average age at diagnosis: 34-43 years, when >95% have polyps

Age	Individuals with colon cancer
21	7%
45	87%
50	93%

From: http://www.gastro.org

Consequences of FAP

- ~50-90% develop small bowel polyps
  - lifetime risk of small bowel malignancy is 4-12%
- ~50% develop gastric polyps
  - ~10% gastric cancer
- ~10% develop desmoid tumours

MANAGEMENT OF FAP

Familial Adenomatous Polyposis (FAP)		SCREENING RECOMMENDATIONS
Colorectal cancer	100%	Colonoscopy annually, beginning age 10-12 yr
Duodenal or periampullary cancer	5%-10%	Upper GI endoscopy every 1-3 yr, beginning age 20-25 yr
Pancreatic cancer	2%	Possible periodic abdominal ultrasound
Thyroid cancer	2%	Annual thyroid examination
Gastric cancer	<1%	Upper GI endoscopy as for duodenal and periampullary
Central nervous system cancer	<1%	Annual physical examination

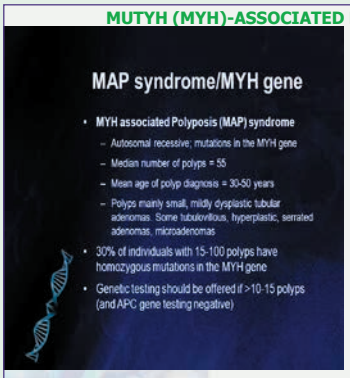
completion proctectomy with or without ileoanal pouch formation is indicated.

- In patients who have had IPAA, the pouch should be examined by flexible endoscopy annually, and a careful digital examination of the anorectal transition zone should be performed.

RECENTLY DESCRIBED SYNDROMES

- **MUTYH (MYH)-Associated Polyposis (MAP)**
- **Serrated Polyposis Syndrome (SPS)**
- **Hereditary Mixed Polyposis Syndrome (HMPS)**
- **Polymerase Proofreading Associated Polyposis [PPAP]**
- **all of these syndromes have an increased risk of colorectal cancer**

MUTYH (MYH)-ASSOCIATED POLYPOSIS (MAP)



- **The *MutY human homologue (MYH)* gene is located on the short arm of chromosome 1, codes for a DNA glycosylase, and is part of the base excision repair (BER) system.**
- **The BER system serves a vital role in the cellular defense against oxidative damage to DNA specifically the oxidation of guanine to 8-oxo-guanine (8-oxoG)**

Patel SG, Ahnen DJ (2012) Familial colon cancer syndromes: an update of a rapidly evolving field. Curr Gastroenterol Rep 14: 428-438

Lucci-Cordisco E, Risio M, Venesio T, Genuardi M (2013) The growing complexity of the intestinal polyposis syndromes. Am J Med Genet A 161: 2777-2787

Cancer Risks with MAP

- Colon cancer: 65-80% (mean age 47)
- Gastric polyps: 11%
- Duodenal polyps: 17%
  - Cancer risk: 4%
- Extraintestinal cancer risks??: up to 38%
  - Includes: ovarian, bladder, skin
  - More???? Breast and uterine???

Screening Recommendations for MAP

- Colonoscopy
  - age 20 years; every 1-2 years
- Upper endoscopy (w side viewing scope)
  - age 30-35 years; every 2 years
- Frequency may be dependent on polyp burden
- Benefit of sulindac (NSAIDs)?

JCN 2014

SERRATED POLYPOSIS SYNDROME (SPS)

- **Key Points**
- **Serrated Polyposis Syndrome (SPS) is a syndrome in which multiple hyperplastic or serrated polyps are identified in the large bowel.**
- **It is estimated that I in 3000 people may have this condition.**
- **This syndrome has been identified in recent years to be associated with an increased risk of developing bowel cancer. Other cancers are not usually associated with this syndrome apart from possibly pancreatic cancer at older ages.**
- **Regular bowel screening by colonoscopy (with removal of polyps) can prevent bowel cancers developing**
- **Colonoscopy is usually performed yearly in the initial years after a diagnosis of SPS. This is to ensure that the polyps can be controlled by removal at colonoscopy. After a few years the interval between procedures may lengthen.**
- **Occasionally bowel surgery is required when polyps are multiple, large and show early signs of bowel cancer.**

SERRATED POLYPOSIS SYNDROME (SPS)

- **Key Points**
- **Cigarette smoking is associated with increased polyp numbers.**
- **SPS is more common in individuals of European or Celtic descent**
- **Up to 50% of individuals with SPS may have a family history of bowel cancer suggesting a possible genetic or inherited cause but this has not been confirmed. Genetic testing is not available.**
- **First degree relatives of individuals with SPS i.e. mother, father, sister, brother, children, have been shown in studies to have a 5 fold increase in their life time risk of developing bowel cancer when compared with the general population.**
- **First degree relatives also have an increased risk of developing SPS**
- **First degree relatives are advised to have 5 yearly bowel screening by colonoscopy from the from the age of 40 years or from an age 10 years younger than the youngest age at which bowel cancer or SPS was identified in the family.**

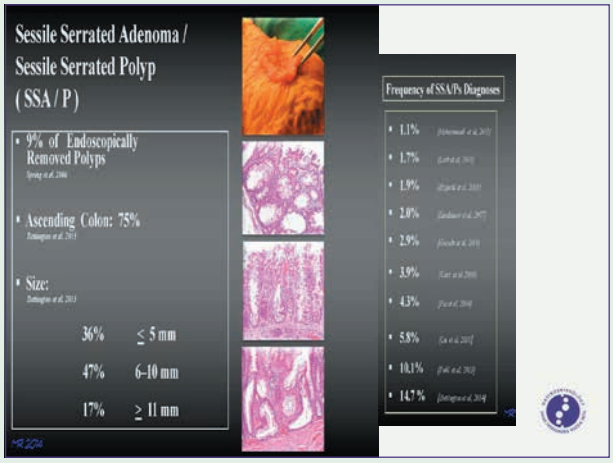
THE WORLD HEALTH ORGANIZATION'S CLINICAL CRITERIA FOR THE IDENTIFICATION OF SERRATED POLYPOSIS

SERRATED POLYPOSIS SYNDROME (SPS), PREVIOUSLY CALLED "HYPERPLASTIC POLYPOSIS SYNDROME,"

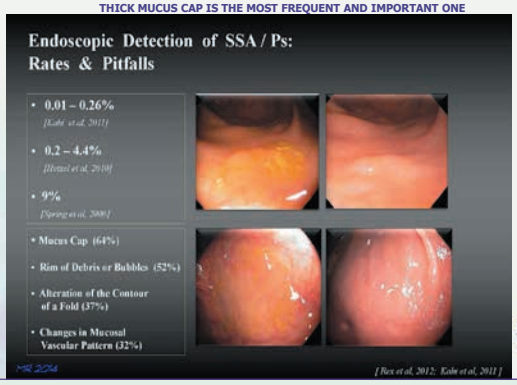
- **Criterion A- At least five serrated polyps proximal to the sigmoid colon, two of which are greater than 10 mm in diameter**
- **Criterion B- Any number of serrated polyps occurring proximal to the sigmoid colon in an individual who has a first-degree relative with serrated polyposis**
- **Criterion C- More than 20 serrated polyps of any size distributed throughout the colon**

A diagnosis of serrated polyposis syndrome can be made if a patient fulfils any of these criteria.

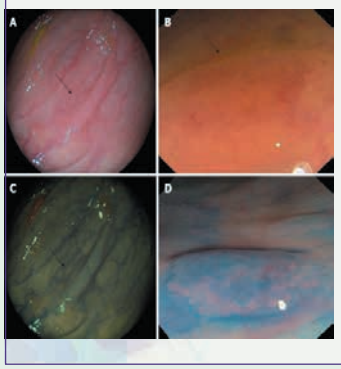
World J Gastroenterol. 2012 May 28; 18(20): 2452–2461.



DETECTION RATES OF SERRATED LESIONS VARY DRAMATICALLY BETWEEN ENDOSCOPISTS, INDICATING THAT THESE LESIONS ARE SIGNIFICANTLY UNDERDIAGNOSED IN CLINICAL PRACTICE. AMONG THE THE PITFALLS IMPAIRING THE DETECTION RATE, THE PRESENCE OF A THICK MUCUS CAP IS THE MOST FREQUENT AND IMPORTANT ONE



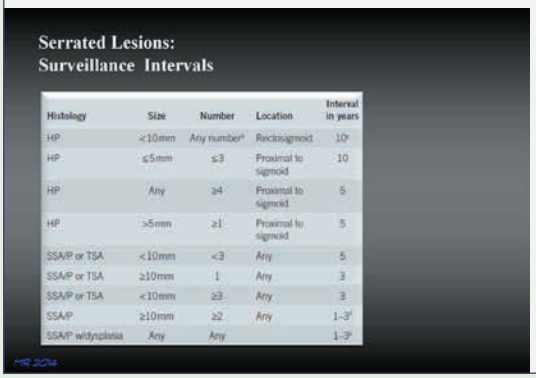
ENDOSCOPIC APPEARANCE OF SERRATED POLYPS



- Endoscopic appearance of serrated polyps. A and B: Sessile serrated adenoma (SSA) (arrows) as flat polyp on conventional optical colonoscopy; C: Narrow-band imaging appearance of polyp (arrow) seen in panel A; D: Chromoendoscopy image of SSA revealing

  Kudo II pattern

SHORTENED (3-5 YEARS) SURVEILLANCE INTERVALS AFTER ENDOSCOPIC RESECTION ARE THEREFORE RECOMMENDED.



HEREDITARY MIXED POLYPOSIS SYNDROME (HMPS)

- Hereditary mixed polyposis syndrome (HMPS)is autosomal dominantly inherited, characterized by the presence of polyps of several different types and/or individual polyps that are composed of more than one histologic type (the most common polyp type is the hamartomatous juvenile polyp, may have a serrated and villiform architecture, may or may not harbor dysplasia; conventional adenomatous polyps also occur
- The polyps are confined to the colon, are between 1-15 in number (and rarely exceed 50), and may resemble adenomas macroscopically
- No extracolonic features have been identified.
- This syndrome is easily confused and clinically overlaps with HMPS and JPS

Lucci-Cordisco E, Risio M, Venesio T, Genuardi M (2013) The growing complexity of the intestinal polyposis syndromes. Am J Med Genet A 161: 2777-2787.

GENETICS, AND CLINICAL MANAGEMENT- (HMPS)

- This syndrome is restricted to one large and extended Ashkenazi Jewish family and smaller Ashkenazi Jewish families
- Recently, the genetic defect that causes HMPS was identified as 40 kb duplication on the long arm of chromosome 15 upstream from the *GREM1* gene
- The management of these patients is not clearly defined.
- Colonoscopy and polypectomy is recommended every 1-2 years and due to the proximal location of many polyps, sigmoidoscopy has no role in surveillance

Jaeger E, Leedham S, Lewis A, Segditsas S, Becker M, et al. (2012) Hereditary mixed polyposis syndrome is caused by a 40-kb upstream duplication that leads to increased and ectopic expression of the BMP antagonist GREM1. Nat Genet 44: 699-703.

POLYMERASE PROOFREADING ASSOCIATED POLYPOSIS (PPAP)

- primarily adenomatous polyposis syndrome,polymerase proofreading associated polyposis (PPAP) is:
- autosomal dominantly inherited polyposis syndrome
- with a variable phenotype that may include 10-100 adenomas
- often presenting before 60-years, with or without colorectal carcinoma
- and/or isolated early onset colorectal carcinoma

Palles C, Cazier JB, Howarth KM, Domingo E, Jones AM, et al. (2013) Germline mutations affecting the proofreading domains of POLE and POLD1 predispose to colorectal adenomas and carcinomas. Nat Genet 45: 136-144.

GENETICS AND CLINICAL MANAGEMENT OF PPAP

- Monoallelic germline mutation of the DNA polymerase subunit genes *POLD1* and *POLE* were identified
- The *POLD1* mutation (S478N) variant predisposes to colorectal cancer, endometrial cancer, and possibly, brain tumors
- regular and frequent colonoscopic polypectomy and consideration of prophylactic surgery in a manner between the recommendations for Lynch syndrome and MAP

Palles C, Cazier JB, Howarth KM, Domingo E, Jones AM, et al. (2013) Germline mutations affecting the proofreading domains of POLE and POLD1 predispose to colorectal adenomas and carcinomas. Nat Genet 45: 136-144.

Briggs S, Tomlinson I (2013) Germline and somatic polymerase Îµ and Î´ mutations define a new class of hypermutated colorectal and endometrial cancers. J Pathol 230: 148-153.

TAKE HOME MESSAGE

- Participation of HPS in epidemiology of CRC does not play a key role (only 5%) but in some of them the occurence of CRC is very expressive (100% or nearly to 100%)
- To have a suspicion on dg of HPS in case of finding 5 polyps or more, younger age (below 45 y)
- Genetic testing that is currently available does not identify a mutation in every case. A gene mutation is not need for dg
- Clinical picture- overlaping
- Thorough surveillance is needed

THANK YOU FOR YOUR ATTENTION

OTHER RESOURCES

- Ian Tomlinson An update on the molecular pathology of the intestinal polyposis syndromes, Diagnostic Histopathol,Volume 21, Issue 4, Pages 147–151, 2015

IBD AS A RISK FACTOR FOR COLORECTAL CARCINOMA. A REAL THREAT OR MORE LIKELY FICTION AT THIS TIME?

Lubomir JURGOS

Jurgos s. r. o., Private Outpatient Department of Gastroenterology, Poliklinika Mytna 5, Bratislava; Slovakia

Inflammatory bowel disease (IBD) requires clinical monitoring and long-term treatment in order to achieve remission and to prevent relapse and colorectal carcinoma (CRC). Patients with IBD have an increased risk of 10–15% for the development of CRC, which is a complication of high economic costs in developed countries.

In contrast to clinical and pathogenetic differences, there is little known about how prognosis differs between these patients and those of sporadic CRC. In a subgroup analysis of UC patients with CRC, female sex was significantly better prognostic factor. This finding implies that estrogens may play a protective role in UC-associated carcinogenesis. 5-aminosalicylates as a class have been associated with protective effects against colorectal cancer in Inflammatory Bowel Disease. Only mesalamine at doses higher than 1.2 g per day is currently widely recommended in this setting. *Mesalamine, particularly at doses over 1.2 g per day, produces a modest reduction in the risk of CRC in IBD patients.* Sulfasalazine does not seem to reduce the risk of colorectal carcinoma. Authors from Denmark and France used MEDLINE, EMBASE and Cochrane databases from international relevant literature. Meta-analysis did not find a significant protective effect of treatment with thiopurines on the risk of CRC in patients with IBD. Colonoscopic surveillance may have a significant role in the reduction of the risk of advanced and interval CRC. Given the ongoing risk of early CRC, patients with any grade of dysplasia who are managed endoscopically, should be closely monitored with advanced techniques. In patients with IBD, the intestinal microbiota plays a fundamental role in their health status and in the progression of complications or CRC. Mucus seems to play an important role in protecting the intestinal mucosa and in maintaining its integrity. Japan investigators from Kyoto referred about agonist for EP_4-receptor, a prostagladin E_2-receptor subtype, which appear to be a promising therapeutic strategy for UC due to their anti-inflammatory and epithelial regeneration activities. Recently there was identified KAG-308 as an orally-available EP_4-selective agonist. Investigators compared KAG-308 and sulfasalazine for the prevention of colitis and promoting mucosal healing in a mouse model. Results indicated that orally administered KAG-308 suppressed colitis development and promoted mucosal healing. Moreover, this substance exhibited preventive effects on colorectal carcinogenesis, and thus may be a new therapeutic strategy for the management of IBD that confers a reduction of colorectal carcinogenesis.

Conclusion. Colonoscopy surveillance programs are recommended to reduce the risk of CRC and 5-aminosalicylates might represent a favourable therapeutic option for chemoprevention of CRC. ECCO guidelines recommend 5-ASA long term use, as this treatment may decrease the incidence of CRC in ulcerative colitis.

Jurgos L. IBD as a risk factor for colorectal carcinoma. A real threat or more likely fiction at this time? In: *11th International Symposium of Gastroenterology, Saint Petersburg, Russia, 12–14 May 2016*. [online]. Available from URL: http://www.promedcs.eu/sites/default/files/abstractbook_2016.pdf

11th International Symposium of GASTROENTEROLOGY
12–14 May 2016, Saint Petersburg, Russia

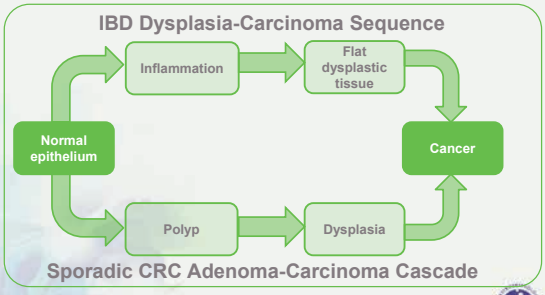
IBD as a risk factor for colorectal carcinoma. The real threat or more likely a fiction at this time.

Lubomir Jurgos, Prof. MD.

Department of Gastroenterology
Poliklinika Mýtna 5, Bratislava

SLOVAKIA

PROGRESSION OF IBD TO CRC



CD, Crohn's disease; CRC, colorectal cancer; IBD, inflammatory bowel disease; UC, ulcerative colitis.

1. Hill MJ et al. *Lancet*. 1978;1:245–247.
2. Hill MJ. *Recent Results Cancer Res*. 1991;122:71–84.
3. Beggs AD et al. *Curr Genomics*. 2008;9:1–10.
4. Lakatos PL et al. *World J Gastroenterol*. 2008;14:3937–3947.

CRC RISK IN IBD

Established Risk Factors

- Young age at the onset of IBD[1]
- Extensive colonic involvement[1]
- Long disease duration (>8-10 years)[1]
- Severity of inflammation[2,3]
- Concomitant inflammatory manifestations – PSC[1]
- Genetic susceptibility – FAP, HNPCC[4]
- Cytokines and growth factors released during inflammation[2]
- Family history of CRC[1]
- Smoking[4]
- Presence of pseudopolyps[2]
- Backwash ileitis[2]

CRC, colorectal cancer; FAP, familial adenomatous polyposis; HNPCC, hereditary non-polyposis colorectal cancer; IBD, inflammatory bowel disease; PSC, primary sclerosing cholangitis.

1. Lukas M. *Dig Dis*. 2010;28(4–5):619–624.
2. Broomé U et al. *Gut*. 1996;38:610–615.
3. Triantafillidis JK et al. *Anticancer Res*. 2009;29(7):2727–2737
4. National Health Service Web site. http://www.nhs.uk/Conditions/Cancer-of-the-colon-rectum or-bowel/Pages/Causes.aspx. Accessed on May 21, 2013.

COMPARISON OF CRC RISK IN PATIENTS WITH CD AND UC: A POPULATION-BASED COHORT STUDY

Study Design	A population-based cohort study
Objective	To compare CRC risk in patients with CD and UC
Patients	• CD cohort – 281 patients from the West Midlands region aged ≥ 15 years, within 5 years of symptom onset; 125 of these patients had extensive colitis* • UC cohort – 823 patients from Birmingham, Oxford and Stockholm aged ≥15 years, within 5 years of symptom onset; 486 of these patients had extensive colitis

*Disease involving the whole colon.

CD, Crohn's disease; CRC, colorectal cancer; UC, ulcerative colitis.TT

Gillen CD et al. *Gut*. 1994;35:1590–1592.

CRC RISK IN EXTENSIVE COLITIS

Extensive Colitis: CRC Morbidity 5+ Years From Onset (Corrected for Operation)

	Site	Observed Cancers	Expected Cancers	RR	95% CI
UC (n = 486)	Colon	22	0.90	24.4***	1.53–37.0
	Rectum	7	0.61	11.5***	4.6–23.6
	Total	29	1.51	19.2***	12.9–27.5
CD (n = 125)	Colon	6	0.16	37.5***	13.7–81.6
	Rectum	2	0.28	7.1*	0.8–25.8
	Total	8	0.44	18.2***	7.8–35.8

*p<0.05, ***p<0.001

CD, Crohn's disease; CI, confidence interval; CRC, colorectal cancer; RR, relative risk; UC, ulcerative colitis.

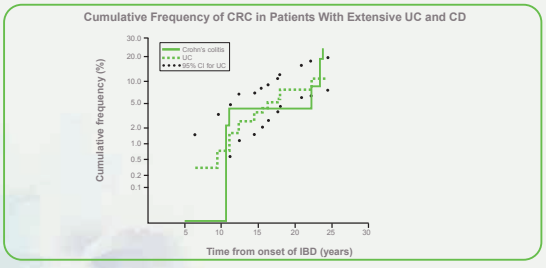
Gillen CD et al. *Gut*. 1994;35:1590–1592.

PATIENTS WITH EXTENSIVE UC AND CD INCREASED RISK FOR CRC

- Patients with extensive CD: 18-fold increased CRC risk
- Patients with extensive UC: 19-fold increased CRC risk
- Young age of onset (< 25 years): Higher relative CRC risk in patients with UC and CD
- CRC risk is lower in patients with CD, as patients undergo colectomy at an early stage of the disease

Gillen CD et al. *Gut*. 1994;35:1590–1592.

CRC RISK IN PATIENTS WITH EXTENSIVE UC AND CD OVER TIME



- Absolute cumulative frequency of CRC
  - Patients with extensive UC: 7% at 20 years from onset
  - Patients with extensive CD: 8% at 22 years from onset

Gillen CD et al. *Gut*. 1994;35:1590–1592.

CRC RISK IN PATIENTS WITH EXTENSIVE CD: EVIDENCE FROM META-ANALYSIS

Parameter	Results (95% CI)
Overall incidence of CD-associated colorectal cancer	0.5/1000 pyd (0.3/1000–0.6/1000)
Overall prevalence of CD-associated colorectal cancer	0.24% (0.19–0.28)
Mean patient age at diagnosis of CD	33.3 years (31.5–35.1)
Mean age at CRC diagnosis	51.5 years (51.4–51.6)
Pooled incidence of CRC in patients having involvement of both small bowel and colon	0.4/1000 pyd (95% CI, 0.3/1000–0.6/1000)
Pooled incidence of CRC in patients having involvement of colon	0.4/1000 pyd (95% CI, 0.3/1000–0.5/1000)

- Patients with CD are at 2–3 times higher risk of CRC
- Age of onset of CRC was reported to be about 20 years earlier in these patients

CI, confidence interval; pyd, persons year duration.

Laukoetter MG et al. *J Gastrointest Surg*. 2011;15(4):576–583.

CRC RISK IN PATIENTS WITH EXTENSIVE UC: EVIDENCE FROM META-ANALYSIS

- 1.6% of patients with UC were diagnosed with CRC during 7–24 years of follow-up with cumulative SIR: 2.4 (95% CI, 2.1–2.7)
- Men were at a higher risk compared with women [SIR, 2.6 (95% CI, 2.2–3.0) vs. 1.9 (95% CI, 1.5–2.3)]
- Other risk factors
  - Young age of onset: SIR, 8.6 (95% CI, 3.8–19.5)
  - Extensive colitis: SIR, 4.8 (95% CI, 3.9–5.9)

- Patients with UC are at 2.4 times higher risk of CRC
- Male sex, young age of onset and extensive colitis are the risk factors associated with CRC development

CI, confidence interval; SIR, standardised incidence ratio;

Jess T. *Clin Gastroenterol Hepatol.* 2012;10(6):639–645.

CHEMOPREVENTION OF CRC

Salicylate[1,2]
- ↓CRC adenomas[5]
- E.g. Aspirin

5-ASA[3,5]
- ↓CRC adenomas
- ↓Cell proliferation
- ↑Apoptosis
- E.g. 5-ASA

NSAIDs[4,5]
- ↓CRC adenomas
- E.g. Sulindac

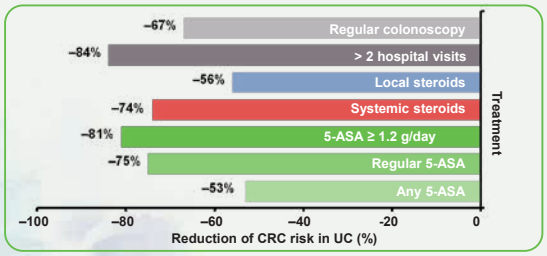
5-FU[6]
- Blocks enzymes of cancerous cells thus slows down/ arrests their growth

MAB[6]
- ↓Growth of cancerous cells
- E.g. Cetuximab

5-ASA, 5-aminosalicylic acid; 5-FU, 5-fluorouracil; CRC, colorectal cancer; MAB, monoclonal antibody; NSAID, non-steroidal anti-inflammatory drug.

1. Thun MJ *et al. N Engl J Med.* 1991;325:1593–1596.
2. Kune GA *et al. Cancer Res.* 1988;48:4399–4404.
3. Allgayer H *et al. Scand J Gastroenterol.* 2002;37:125–131.
4. Giardiello FM *et al. N Engl J Med.* 1993;328:1313–1316.
5. Reddy BS. *Cancer Epidemiol Biomarkers Prev.* 2000;9:239–247.
6. Bowel Cancer UK Web site. http://www.bowelcancer.uk.org/living-with-and-beyond/treatment-options/chemotherapy-drugs-for-bowel-cancer/. Accessed May 21, 2013.

EFFICACY OF 5-ASA IN CRC PREVENTION IN PATIENTS WITH UC: A CASE-CONTROL STUDY (CONT'D)



- Regular treatment with 5-ASA reduces the CRC risk to a great extent
- After adjustment of other variables, 5-ASA leads to 81% reduction in CRC risk, the protective effect being evident at a dose of ≥ 1.2 g/day

Eaden JA *et al. Aliment Pharmacol Ther.* 2000;14:145–153.

5-ASA: MECHANISMS OF ACTION

Activates
- PPAR-γ[1]
- Cell cycle checkpoint[5]

Inhibits
- Colonic epithelial cell proliferation[1]
- β-catenin[2], EGFR signalling[3]
- NF-κB, MMPs, TNF-α and COX-2[4]

5-ASA, 5-aminosalicylic acid; COX, cyclooxygenase; COX-2, cyclooxygenase 2; EGFR, epithelial growth factor receptor; MMPs, matrix metalloproteinases; NF-κB, nuclear factor kappa beta; PG, prostaglandin; PPAR-γ, peroxisome proliferator activated receptor-gamma; TNF-α, tumour necrosis factor alpha.

1. Williams C *et al. Therap Adv Gastroenterol.* 2011;4(4):237–248.
2. Bos CL *et al. Carcinogenesis.* 2006;27:2371–2382.
3. Monteleone G *et al. Cell Death Differ.* 2006;13:202–211.
4. Lyakhovich A *et al. Aliment Pharmacol Ther.* 2010;31(2):202–209.
5. Reinacher-Schick A *et al. Carcinogenesis.* 2003;24:443–451.

5-ASA: MECHANISMS OF ACTION (CONT'D)

Increases
- Apoptosis[1]
- Replication fidelity[2,3]
- Intercellular cell adhesion of HT29 and HCT116 cells[4]

Decreases
- NF- κB, IL-1β, NF-κB, IκB kinase production[1,5]
- Cell proliferation[1]
- PAK1[4]
- TGF-β signalling[5]

Others
- Stabilises microsatellites[1]
- Oxygen scavenger[6]
- Replication of checkpoints in CRC cells[7]
- Induction of E-cadherin[4]
- Antimicrobial (antibacterial) activity[5]

5-ASA, 5-aminosalicylic acid; CRC, colorectal cancer; IκB, I kappa beta; IL-1β, interleukin 1 beta; NF-κB, nuclear factor kappa beta; PAK1, p21 activated kinase 1; TGF-β, transforming growth factor beta.

1. Williams C *et al. Therap Adv Gastroenterol.* 2011;4(4):237–248.
2. Luciani MG *et al. Gastroenterology.* 2007;132:221–235.
3. Gasche C *et al. Cancer Res.* 2000;60:3993–3997.
4. Khare V *et al. Biochem Pharmacol.* 2013;85(2):234–244.
5. Lyakhovich A *et al. Aliment Pharmacol Ther.* 2010;31(2):202–209.
6. Joshi R *et al. Free Radic Res.* 2005;39:1163–1172.
7. Stolfi C *et al. J Biomed Biotechnol.* 2012;2012:980458.

5-ASA ACTIVITY IN CELL CYCLE OF CRC CELLS: EVIDENCE FROM IN-VITRO STUDIES

- At a concentration of ≥ 20 mM, 5-ASA significantly interferes with the cell cycle of colorectal cancer cells
- After 24 hours of incubation with 5-ASA at concentrations of > 35 mM, cell proliferation levels are reduced even below the starting values, suggesting induction of apoptosis
- Encourages cell death in the form of apoptosis, necrosis and mitotic catastrophe, hence attaining the indispensable goal of cancer therapy

Koelink PJ *et al. Inflamm Bowel Dis.* 2010;16(3):379–389.

5-ASA REDUCED CRC RISK IN PATIENTS WITH IBD

Drug	Dose (g)	Reduction of CRC Risk (%)
5-ASA[1]	≥ 1.2	81
Various 5-ASA[2]	1.5–4	75
Sulphasalazine[3]	1.5–3	62
Various 5-ASA[4]	≥ 1.2	72
Various 5-ASA[5]	Various	33 overall (49 with regular use > 2 years)
Sulphasalazine[6]	Various	66
Various 5-ASA[7]	Various	NS

5-ASA, 5-aminosalicylic acid; CRC, colorectal cancer; IBD, inflammatory bowel disease; NS, not significant.

1. Eaden J *et al. Aliment Pharmacol Ther.* 2000;14:145–153.
2. Pinczowski D *et al. Gastroenterology.* 1994;107:117–120.
3. Moody GA *et al. Eur J Gastroenterol Hepatol.* 1996;8:1179–1183.
4. Rubin DT *et al. Inflamm Bowel Dis.* 2008;14:265–274.
5. van Staa TP *et al. Gut.* 2005;54:1573–1578.
6. Croog VJ *et al. Int J Colorectal Dis.* 2003;18:392–400.
7. Bernstein CN *et al. Am J Gastroenterol.* 2003;98:2784–2788.

EFFECT OF 5-ASA ON CRC RISK

5-ASA reduces CRC risk

CRC, colorectal cancer.
Munkholm P. *Aliment Pharmacol Ther.* 2003;18(suppl 2):1–5.

EFFICACY OF 5-ASA IN CRC PREVENTION IN PATIENTS WITH UC: A CASE-CONTROL STUDY

Objective	• To assess the possible risk factors responsible for the development of CRC in patients with UC • To develop a statistical model for determining the most harmful combination of the risk factors
Study Design	Retrospective matched, case-controlled study
Number of Patients	102 cases of CRC in UC compared with matched controls

CRC, colorectal cancer; UC, ulcerative colitis.

Eaden JA et al. *Aliment Pharmacol Ther.* 2000;14:145–153.

EFFICACY OF 5-ASA IN CRC PREVENTION IN PATIENTS WITH UC: A CASE-CONTROL STUDY (CONT'D)

- Results
  - Regular use of 5-ASA: 75% reduction in CRC risk (OR: 0.25; 95% CI: 0.13–0.48; p < 0.00001) compared with controls
  - Compared with no treatment, 5-ASA at a dose of ≥ 1.2 g/day lowered CRC risk by 91% (OR 0.09, 95% CI: 0.03–0.28, p < 0.00001)
  - After adjustment for other variables: 81% reduction in CRC risk with regular 5-ASA ≥ 1.2 g/day (OR: 0.19 95% CI: 0.06–0.61; p = 0.006)
  - Sulphasalazine was effective only at a dose of ≥2 g/day (OR 0.41, 95% CI: 0.18–0.92, p = 0.03)
  - > 2 regular visits to a hospital doctor led to 84% reduction in CRC risk
  - Family history of sporadic CRC increased the CRC risk by 5 times (OR 5.0, 95% CI 1.10–22.82, p < 0.04).

- **Regular treatment with 5-ASA reduces the CRC risk to a great extent**
- **After adjustment of other variables, 5-ASA leads to 81% reduction in CRC risk, the protective effect being evident at a dose of ≥ 1.2 g/day**

5-ASA, 5-aminosalicylic acid; CI, confidence interval; CRC, colorectal cancer; OR, odds ratio; UC, ulcerative colitis.

Eaden JA et al. *Aliment Pharmacol Ther.* 2000;14:145–153.

5-ASA USE AND CRC RISK IN IBD: A LARGE EPIDEMIOLOGICAL STUDY

Objectives	• To evaluate the effect of regular use of 5-ASA on CRC risk reduction in a large database of patients with IBD in addition to the prospective recording of drug prescribing • To evaluate the effect of regular use of oral glucocorticoids or immunosuppressants on CRC risk
Study Design	Case-controlled, large epidemiological study
Number of Patients	Cohort of 18,969 patients assigned to the 5-ASA/IBD group (100 patients who developed CRC as a result of exposure to 5-ASA)

5-ASA, 5-aminosalicylic acid; CRC, colorectal cancer; IBD, inflammatory bowel disease; UC, ulcerative colitis.

van Staa TP et al. *Gut.* 2005;54:1573–1578.

5-ASA USE AND CRC RISK IN IBD: A LARGE EPIDEMIOLOGICAL STUDY (CONT'D)

Reduced CRC risk in regular users (≥ 6 5-ASA prescriptions in the last 12 months) compared with irregular users (OR: 0.7; 95% CI: 0.44–1.03)

Regular 5-ASA users: 6–12 prescriptions (OR: 1.13; 95% CI: 0.49–2.59); 13–30 prescriptions (OR: 0.30; 95% CI: 0.11–0.83); >30 prescriptions (OR: 0.31; 95% CI: 0.11–0.84)

Regular use of oral glucocorticoids or immunosuppressants was also associated with a reduced risk of CRC compared with irregular use [crude OR: 0.51 (95% CI, 0.27–0.98); adjusted OR: 0.38 (95% CI, 0.18–0.80)]

Regular treatment with 5-ASA reduces the CRC risk when compared with irregular users, the effect being consistent for 5-ASA

5-ASA, 5-aminosalicylic acid; CI, confidence interval; CRC, colorectal cancer; IBD, inflammatory bowel disease; OR, odds ratio.

van Staa TP et al. *Gut.* 2005;54:1573–1578.

EFFECT OF 5-ASA ON CRC IN PATIENTS WITH IBD: A CASE-CONTROLLED STUDY

Objective	To evaluate the effect of various risk factors on establishment of CRC in patients with IBD
Study Design	Retrospective, case-controlled, cohort study
Number of Patients	Cohort of 1,594 patients (30 CRC patients)

CRC, colorectal cancer; IBD, inflammatory bowel disease.

Tang J et al. *Dig Dis Sci.* 2010;55(6):1696–1703.

EFFECT OF 5-ASA ON CRC IN PATIENTS WITH IBD: A CASE-CONTROLLED STUDY (CONT'D)

Results

- Results of multivariate analysis showed that there was a reduction in CRC risk by 97.6% in patients who received 5-ASA at a cumulative dose of ≥ 4.5 g (p = 0.047)

Regular treatment with 5-ASA reduces the CRC risk in UC when compared with irregular users

CRC, colorectal cancer; IBD, inflammatory bowel disease; UC, ulcerative colitis.

Tang J et al. *Dig Dis Sci.* 2010;55(6):1696–1703.

CONCLUSION

- Patients with IBD are at increased risk of CRC[1]
  - Patients with extensive CD: 18-fold increased CRC risk
  - Patients with extensive UC: 19-fold increased CRC risk
- Chemotherapy of CRC included NSAIDs, 5-FU and MABs and chemoprophylaxis included salicylates, 5-ASA.[2–7]
- 5-ASA (≥ 20 mM) induces and increases apoptosis in CRC cells[8]
- Regular use of 5-ASA > 1.2 g/day significantly reduces CRC risk[9]
- However, some of these results were inconsistent and limited by heterogeneity involved[11]

5-ASA, 5-amino salicylic acid; 5-FU, 5-fluorouracil; CD, Crohn's disease; CRC, colorectal cancer; IBD, inflammatory bowel disease; MABs, monoclonal antibodies; NSAIDs, non-steroidal anti-inflammatory drugs; UC, ulcerative colitis.

1. Gillen CD et al. *Gut.* 1994;35:1590–1592.
2. Thun MJ et al. *N Engl J Med.* 1991;325:1593–1596.
3. Kune GA et al. *Cancer Res.* 1988;48:4399–4404.
4. Allgayer H et al. *Scand J Gastroenterol.* 2002;37:125–131.
5. Giardiello FM et al. *N Engl J Med.* 1993;328:1313–1316.
6. Reddy BS. *Cancer Epidemiol Biomarkers Prev.* 2000;9:239–247.
7. Bowel Cancer UK Web site. http://www.bowelcanceruk.org.uk/living-with-and-beyond/treatment-options/chemotherapy-drugs-for-bowel-cancer/. Accessed May 21, 2013.
8. Kostrik PJ et al. *Inflamm Bowel Dis.* 2010;16(3):379–389.
9. Eaden JA et al. *Aliment Pharmacol Ther.* 2000;14:145–153.
10. Bernstein CN et al. *Am J Gastroenterol.* 2011;106(4):731–736.
11. Nguyen GC et al. *Am J Gastroenterol.* 2012;107(9):1298–1304.

Future

agonist EP4 receptor and receptor subtype prostagladin E2
UC – promote mucosal healing
KAG-308
EP4 – orally avalaible selective agonist (mouse model)
promising theraputic strategy for UC

Take home message

– colonoscopy surveillance programs

– 5-aminosalicylates longterm use decrease incidence CRC in UC
(ECCO guidelines, 2015)

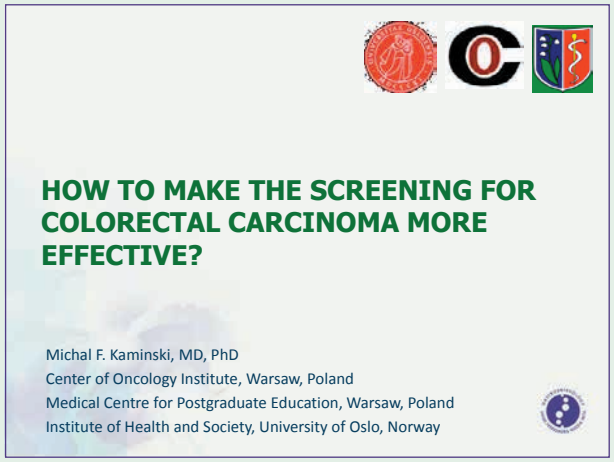
HOW TO MAKE THE SCREENING FOR COLORECTAL CARCINOMA MORE EFFECTIVE

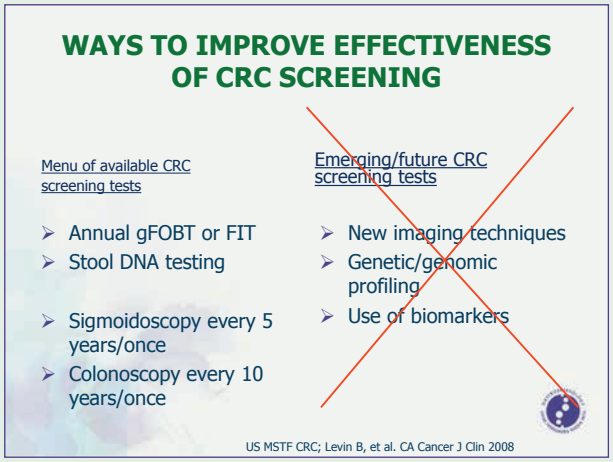
Michal KAMINSKI

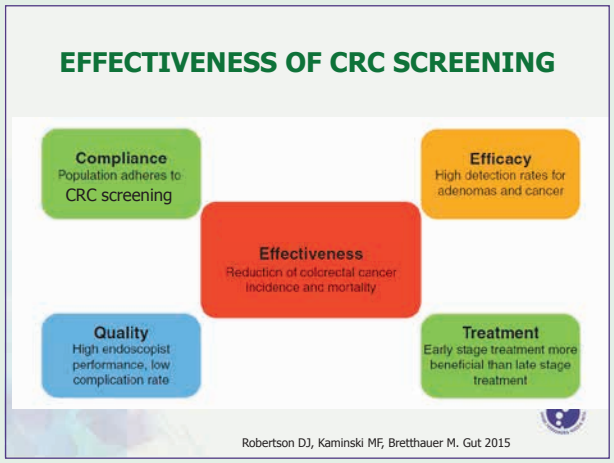
Department of Gastroenterology, Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw; Poland

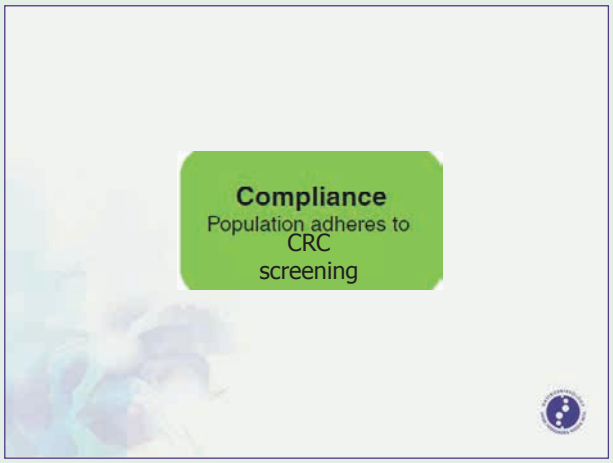
Effectiveness of colorectal cancer screening is measured with the effect on colorectal cancer mortality and incidence. The effectiveness of screening is determined by four major factors: compliance with a screening test, efficacy of a screening test to detect precursor lesions and cancers, low complication rates and efficacy of treatment of screen detected lesions. In order to make screening for colorectal cancer more effective all these four driving factors have to be optimized. This talk aims to summarize available evidence on the methods to optimize compliance, efficacy of screening test, efficacy of treatment and complication rates.

Kaminski M. How to make the screening for colorectal carcinoma more effective. In: *11th International Symposium of Gastroenterology, Saint Petersburg, Russia, 12–14 May 2016*. [online].
Available from URL: http://www.promedcs.eu/sites/default/files/abstractbook_2016.pdf



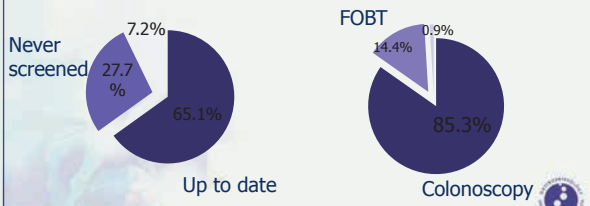






COMPLIANCE WITH CRC SCREENING

- Compliance across countries/programs: 10-90%
- Compliance with CRC screening in the US:



Centers for Disease Control and Prevention, US, 2013
Schreuders H, et al. Gut 2015

INTERVENTIONS TO PROMOTE COMPLIANCE WITH CRC SCREENING – POLICY LEVEL

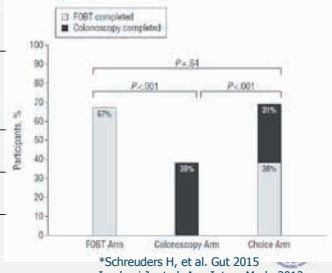
1. Implementation of organized program
   - Reduced financial barriers
   - Active invitation of entire target population
   - Reminders to non-responders
   - Follow-up of screen positive results

Senore C, et al. BEGA 2010
Segnan N, et al. IARC/WHO guidelines, 2010

INTERVENTIONS TO PROMOTE COMPLIANCE WITH CRC SCREENING – POLICY LEVEL

2. Choice of the screening test

	Partcipation rate*
gFOBT	16-67%
FIT	17-77%
FS	30-84%
CS	16-93%



*Schreuders H, et al. Gut 2015
Inadomi J, et al. Ann Intern Med., 2012

INTERVENTIONS TO PROMOTE COMPLIANCE WITH CRC SCREENING – PROVIDER LEVEL

1. Involvement of primary care providers

	Compliance rate	Unsedated colonoscopy rate
Informational leaflet	13.7%	39.0%
Active counselling	47.0%	77.0%

Boguradzka A, et al. Scand J Gastro 2014

INTERVENTIONS TO PROMOTE COMPLIANCE WITH CRC SCREENING – PARTICIPANT LEVEL

1. Increasing individual awareness
   - Informational (enhanced) leaflets
   - Advanced notification letters
   - Promotional campaings (limited)
   - Patient navigation (opportunistic)

Senore C, et al. BEGA 2010
Segnan N, et al. IARC/WHO guidelines, 201

Efficacy
High detection rates for adenomas and cancer

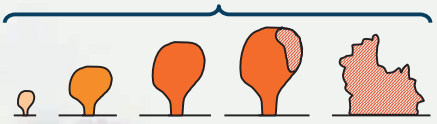
EFFICACY OF CRC SCREENING

	gFOBT	FIT	FS	CS
Sensitivity for advanced neoplasia	9-24%	32-53%	90-92%	88-98%
Sensitivity for CRC	13-50%	79%	90-92%	92-99%

Schreuders H, et al. Gut 2015

EFFICACY OF CRC SCREENING - CRC PREVENTION VS EARLY DETECTION

Colonoscopy, Sigmoidoscopy

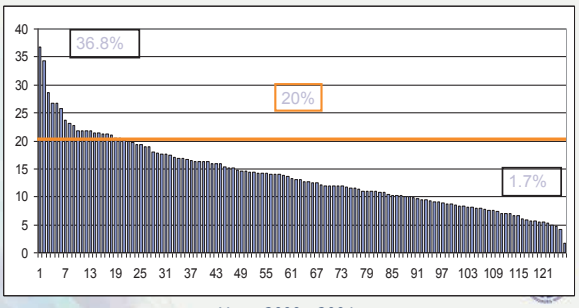


gFOBT, FIT

*Winawer SJ, et al. NEJM 1993

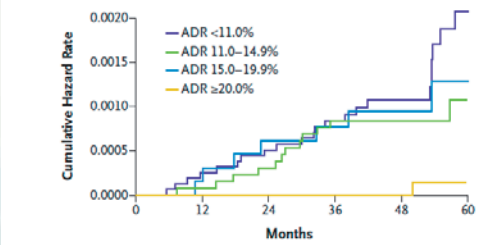
Quality
High endoscopist performance, low complication rate

VARIABLE QUALITY
ADENOMA DETECTION RATE BY ENDOSCOPIST



Years 2000 - 2004

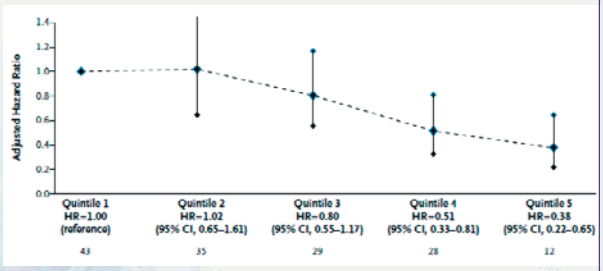
CUMULATIVE HAZARD RATES FOR INTERVAL CRC - ACCORDING TO ENDOSCOPIST'S ADR



No. at Risk						
ADR <11.0%	15,883	15,805	15,744	15,669	9355	4717
ADR 11.0–14.9%	13,281	13,223	13,182	13,120	7571	4003
ADR 15.0–19.9%	6,607	6,582	6,562	6,539	4022	2529
ADR ≥20.0%	9,255	9,235	9,202	9,166	7155	5548

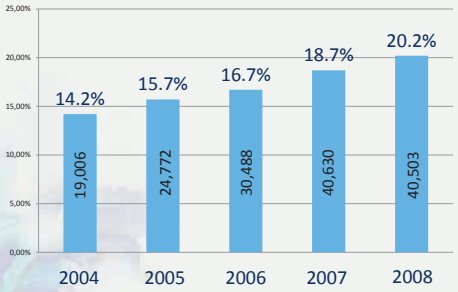
Kaminski, Regula et al. NEJM, 2010

HAZARD RATIOS FOR FATAL CRC ACCORDING TO ADR



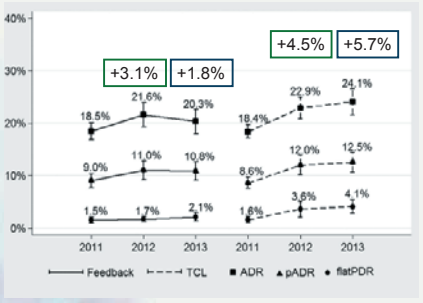
Corley DA, et al. NEJM, 2014

ADR IMPROVEMENT WITH MONITORING AND FEEDBACK



Kaminski MF, et al. DDW 2015

TRAIN CSPY LEADERS VS FEEDBACK - EFFECT ON LEADERS AND CENTERS PERFORMANCE

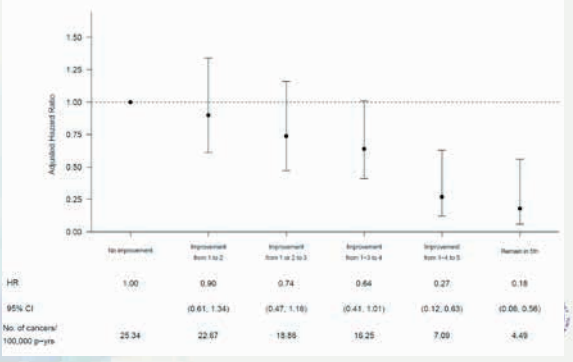


OR (95%CI)
1.25 (1.04-1.50)*
1.23 (0.97-1.55)
1.76 (1.11-2.82)*
p ≤ 0.017

* Late post-intervention phase vs. Pre-intervention phase

Kaminski MF, et al. Gut 2015

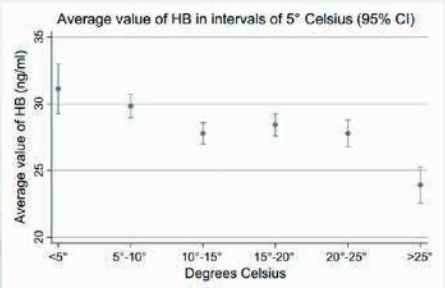
ADJUSTED HAZARD RATES FOR INTERVAL CRC BY ADR IMPROVEMENT CATEGORY



HR	1.00	0.90	0.74	0.64	0.27	0.18
95% CI		(0.61, 1.34)	(0.47, 1.16)	(0.41, 1.01)	(0.12, 0.63)	(0.08, 0.56)
No. of cancers/ 100,000 p-yrs	25.34	22.67	18.86	16.25	7.09	4.49

Kaminski, et al. DDW 2015

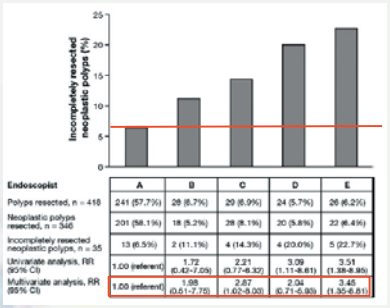
INFLUENCE OF SEASONAL VARIATIONS IN AMBIENT TEMPERATURES ON PERFORMANCE OF FIT



Grazzini *et al.* Gut 2010

Treatment
Early stage treatment more beneficial than late stage treatment

VARIABLE QUALITY OF POLYP REMOVAL BY ENDOSCOPISTS



Endoscopist	A	B	C	D	E
Polyps resected, n = 418	241 (57.7%)	28 (6.7%)	20 (6.9%)	24 (5.7%)	26 (6.2%)
Neoplastic polyps resected, n = 340	201 (58.1%)	18 (5.2%)	28 (8.1%)	20 (5.8%)	22 (6.4%)
Incompletely resected neoplastic polyps, n = 35	13 (6.5%)	2 (11.1%)	4 (14.3%)	4 (20.0%)	5 (22.7%)
Univariate analysis, RR (95% CI)	1.00 (reference)	1.72 (0.42–7.09)	2.21 (0.77–6.32)	3.09 (1.11–8.61)	3.51 (1.38–8.95)
Multivariate analysis, RR (95% CI)	1.00 (reference)	1.98 (0.61–7.75)	2.87 (1.02–8.00)	2.04 (0.71–5.93)	3.45 (1.35–8.81)

Pohl H et al. Gastroenterology 2013

METHODS TO OPTIMIZE POLYP RESECTION

En-bloc resection → Position of endoscope; Distension +/- lifting?; Snare diameter&techniq.

Endoscopist's skills → Training

Margins assesment → Washing; Virtual/Conv. chromo?*; Magnified endoscopy??

*Kaminski MF et al. Endoscopy 2014

DIRECT OBS. OF POLYPECTOMY SKILLS (DOPYS)

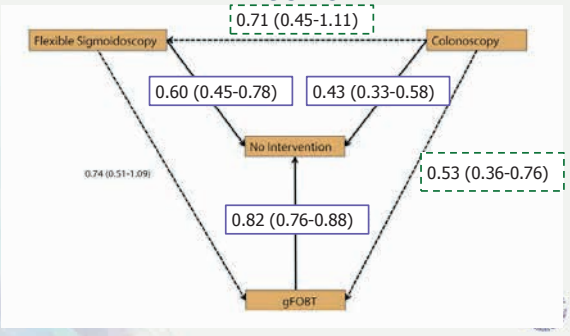
4 point scale: ≥ 3 for competence

- Optimizes polyp position
- Optimises polyp view (distension, washing)
- Determines full extent of the lesion
- Selects appropriate snare size
- Appropriately positions snare
- Identifies residual polyp after resection

Gupta S et al. GIE 2011

Colonoscopy screening
Effectiveness
Reduction of colorectal cancer incidence and mortality

EVIDENCE FOR THE EFFECTIVENESS OF CRC SCREENING - CRC MORTALITY REDUCTION



*RCT and observational studies combined

Elmunzer BJ, et al. Gastrointest Endosc 2015

CONCLUSIONS

Ways to make screening for CRC more effective

- Interventions to promote compliance
- Choice of efficacious screening test
- Quality assurance & improvement initiatives
- Optimized treatment techniques

11th International Symposium of GASTROENTEROLOGY

POSTER PRESENTATION ABSTRACTS

HEPATOCELLULAR CARCINOMA IN CENTRAL SLOVAKIA: COHORT FROM TERTIARY REFERRAL CENTRE

Svetlana ADAMCOVA-SELCANOVA[1], Lubomir SKLADANY[1], Jana BADINKOVA[1], Eva PRITZOVA[2], Stanislav OKAPEC[3]

1. HEGITO (Div. Hepatology, Gastroenterology and Liver transplantation) of Dept. Internal Medicine II, Slovak Medical University; 2. Dept. of Oncology; 3. Dept. of Radiology University Hospital, Banska Bystrica, Slovakia

Introduction. Hepatocellular carcinoma (HCC) from various geographical regions differs significantly in epidemiologic, demographic and clinical characteristics; the aim here was to describe the cohort from tertiary referral centre in Slovakia.

Methodology. Analysis of charts of consecutive patients (pts) seen in Liver unit of regional university hospital (catchment area with 662 121 inhabitants). **Inclusion** criterion: Diagnosis (Dg) of HCC according to EASL guidelines 2001, 2005 and 2006 and EASL-EORTC guidelines 2012 as recorded in electronical database Care Center of Roosevelt hospital. **Exclusion** criterion: Impossibility to retrieve sufficient data for final analysis. Study interval: July, 2007 – Feb, 2015.

Results. Cohort consisted of 161 pts, 95% with liver cirrhosis, 77% men. Median age was 61.2 years (21–86); men: 61 years (41–81), women: 62 years (21–86). **Etiology** of underlying liver disease: ALD – 72 pts (45%); HCV – 27 pts (17%); HBV – 21 pts (13%); NASH – 16 pts (10%); cryptogenic – 13 pts (8%); pts without Ci – 8 (5%); HCV + HBV – 2 pts (1%); hereditary hemochromatosis – 1 pt (0.5%), PBC – 1 (0.5%). Thirty-six cases (23%) were diagnosed by surveillance, other 68% presented as non-surveillance, 9% of pts were unknown. The average of HCC lesions in pts performed by surveillance was 4.6 cm and performed by non-surveillance was 8.3 cm. **BCLC classes:** a) whole cohort: A – 25 pts (16%); B – 40 (25%); C – 65 (40%); D – 31 (19%). b) according to Dg-modality (Dg by surveillance vs. non-surveillance): A – 12/36 (33%) vs. 11/110 (10%); B – 15/36 (42%) vs. 25/110 (23%); C – 6/36 (17%) vs. 48/110 (43%); D – 3/36 (8%) vs. 26/110 (24%). **Treatment:** Surgical resection – 13 pts (7%); liver transplant (LTx) – 12 (6%); RFA – 15 (8%); DEB-TACE – 39 (21%); sorafenib – 76 (40%); best of supportive care – 35 (18%). Data for survival analysis were available for every 161 pts. Median **survival** in whole cohort was 15.9 months (0.25–92.5); survival in BCLC classes: A – 29.5 months (2–92.5); B – 18.7 months (3–69); C – 14.8 months (0.25–81); D – 3.33 months.

Conclusion. 1) Demographics in this cohort resemble those of HCC in western world, except from absence of gender age difference. 2) Alcoholic liver disease was the commonest etiology of underlying liver disease. 3) Its stage was cirrhosis in 95% of cases. 4) The most important finding was that only 23% of HCC cases were detected via surveillance program. 5) There was marked right-sided shift in BCLC distribution with ensuing treatment allocation and survival. 5) One possible explanation of rather good survival in BCLC-C could be the availability of sorafenib.

sselcanova@gmail.com; Phone: +421 918 538 983
lubomir.skladany@gmail.com; Phone: +421 905 482 997

Adamcova-Selcanova S., *et al*. Hepatocellular carcinoma in central Slovakia: Cohort from tertiary referral centre. In: *11th International Symposium of Gastroenterology, Saint Petersburg, Russia, 12–14 May 2016*. [online].
Available from URL: http://www.promedcs.eu/sites/default/files/abstractbook_2016.pdf

PILOT SCREENING OF NAFLD IN PATIENTS WITH OVERWEIGHT/OBESITY AND DIABETES

Maria BELOVICOVA [1,2,3], Ivana FEDORKOVA [1,2], Adriana PHILIPPIOVA [4], Frantisek GRANO [5]

1. Slovak society of practical obesitology (SSPO), Bardejov; 2. Internal ambulance focusing on the diagnostics and treatment of liver diseases, Remedium, s. r. o.; 3. High School of Health and Social Sciences of Saint Elisabeth Bratislava, Bardejov and Michalovce; 4. Diabetic ambulance, Bardejov; 5. PROM.MEDIC.SK spol. s r. o., Bratislava; Slovakia

Introduction. Obesity, together with non-alcoholic fatty liver disease (NAFLD) and diabetes mellitus have increasing worldwide prevalence. Non-alcoholic fatty liver disease (NAFLD) is a broad spectrum of clinical and pathological conditions. The risk factors for the development of NAFLD include: obesity, diabetes mellitus (DM) type 2, hypertriglyceridemia. NAFLD mainly associated with type 2 diabetes and metabolic syndrome is the world's most common chronic disease that affects 15–40% of the world's population. More than 70% of patients with type 2 diabetes mellitus (DM) have at the same time NAFLD.

Methods. Transient elastography (TE) is a non-invasive painless method that measures the liver stiffness. TE evaluates the propagation of the speed shock wave in the liver. With high accuracy TE confirms respectively excludes liver cirrhosis. Investigations are performed on the device Fibroscan 502 touch, in obese patients we use XL probe. As a screening method for liver steatosis we use abdominal ultrasound, including Doppler examination.

Objective. To detect the liver fibrosis through TE in patients with overweight/obesity arriving to internal ambulance for the purpose of differential diagnostics of liver diseases.

Results. From 12/2015 to the end of 1/2016 we examined 150 patients (75 men / 75 women) who are overweight/obese. They arrived to our clinic for elevations of liver transaminases or for finding of hepatic steatosis in ultrasonography. In all patients we realised transient elastography. In 8 patients (5 men / 3 women) we diagnosed impaired glucose tolerance (IGT), type 2 diabetes had a total of 46 patients (20 men / 26 women). Patients with IGT and DM2T accounted for 36% of the group (54/150). The presence of liver fibrosis (F1 or greater) was observed in 50/54 patients (92.6% of the group), the finding of severe liver fibrosis (F2 or greater) was observed in 37/54 patients (20 men / 17 women) with type DM2T, which represents 68.5% of the group. Liver fibrosis was diagnosed in 52.1% patients without DM2T (50/96), severe fibrosis was found only in 25% of the group (24/96). In all patients with the finding of liver fibrosis we performed the differential diagnostics of liver diseases and began complex treatment.

Conclusions. NAFLD is the world's most widely used form of liver damage in adults and children. TE achieves a high level of accuracy in the detection of liver fibrosis in patients with chronic liver diseases. TE can be used in monitoring of patients and also such a screening of chronic liver diseases. Given the high prevalence of NAFLD in patients with DM2T these patients may benefit from screening through transient elastography. Detection of advanced fibrosis or cirrhosis is in patients with type 2 diabetes very important because liver diseases are the fourth leading cause of mortality in patients with diabetes. Interdisciplinary

cooperation of more experts is needed for early diagnostics of NAFLD and avoiding of its late complications.

Supported by PROM.MEDIC.SK spol. s r. o. grant program to Slovak society of practical obesitology (SSPO).

mriab9@gmail.com; Phone: +421 903 447 596

Belovicova M., *et al*. Pilot screening of NAFLD in patients with overweight/obesity and diabetes. In: *11th International Symposium of Gastroenterology, Saint Petersburg, Russia, 12–14 May 2016*. [online].
Available from URL: http://www.promedcs.eu/sites/default/files/abstractbook_2016.pdf

IN SITU SPLIT LIVER RESECTION – A NEW METHOD OF INDUCING REMNANT VOLUME REGENERATION

D. I. SKORYI, O. M. TYSHCHENKO, O. V. MALOSHTAN, T. V. KOZLOVA, A. O. MALOSHTAN, N. M. VOSKRESENSKA

GI "Institute of General and Urgent Surgery of NAMS of Ukraine", HPB Surgery Department, Kharkiv; Ukraine

Introduction. At the time of discovering a disease, liver resection appears to be impossible in a number of cases. One of essential reasons of liver non-resectibility is a small volume of the remnant parenchyma.

Materials and Methods. Patient K., 43. Clinical diagnosis: *hepatocellular carcinoma T3aN0M1 (Hepar) Sg 4, 5, 6, 7, 8, 9. Tumor compression of lobe biliary structures. Obstructive jaundice.*

According to SCT, the liver remnant volume was 136.2 cm^3 – 16.4% of the overall volume not involved in the tumor process. Taking into consideration the extremely low remnant volume and biliary hypertension, in situ split liver resection was scheduled.

1st stage of the surgical procedure. The surgery was performed routinely. J-laparotomy. Inspection results: the size of the liver was expanded through the right lobe in the parenchyma of which two large tumor formations were detected. The left lateral liver section (Sg 2, 3) bore no signs of focal pathology. We performed hepatoportal devascularization of the right liver lobe, transection of the liver parenchyma along the border of the left lateral and medial liver lobes.

2nd stage of the surgical procedure. On the 9th day after the surgery relaparotomy was performed. After division of loose commissures, a haematoma was detected in the space between the left lateral and medial sections. The haematoma volume was up to 250 ml. It was evacuated. The right and medial liver veins were singled out, stitched and intersected. We mobilized the subhepatic segment of the lower vena cava, clipped and intersected short hepatic veins. After total devascularization of the removable part, the right coronary and triangular ligaments were intersected. The right lobe was extracted from the abdominal cavity as a whole block with Sg 4, 9 (right trisection ectomy).

Results. Beginning with the first day after the surgery, bile started running along the drainage pipe up to 80–100 ml a day. Along the drainage system of the abdominal cavity, up to 3.5–4 liters of ascitic fluid was running a day without a tendency for decreasing, which was considered to be a sign of hepatoportal hypertension through stitching the right lobal portal vein. We observed considerable hyperplasia of the left lateral liver section (Sg 2, 3) and increase of the distance between Sg 4 and Sg 2, 3 by 62%. Sg 4 was weakly contrasted, in some areas it was not contrasted at all. Another segmental area of absence of contrasting was also detected in the part of the large-size tumor adjoining S4 segment.

With the therapy provided, the period after the relaparotomy was characterized by slow positive dynamics. The right reactive pleurisy up to 150 ml did not require tapping. The patient was discharged from hospital in a relatively satisfactory state on the 16th day after the

surgery. At present, it has been 1.5 years since the surgery, the patient is in a satisfactory state, we have obtained no information on relapses.

Conclusions. Liver resection in situ split proves to be effective, and in most cases it is the only possible method to treat patients with liver parenchyma affection of over 80% of its volume.

Skoryi D.I., *et al*. In situ split liver resection – A new method of inducing remnant volume regeneration. In: *11th International Symposium of Gastroenterology, Saint Petersburg, Russia, 12–14 May 2016*. [online]. Available from URL: http://www.promedcs.eu/sites/default/files/abstractbook_2016.pdf

PLACE OF APPLICATION INHIBITORS OF THE PROTON PUMP IN TREATMENT OF THE CHRONIC PANCREATITIS

F. I. KHAMRABAEVA

The Tashkent institute of postgraduate medical education, Tashkent; Uzbekistan

Research objective. Studying of clinical efficiency rabeprasole in complex therapy of an aggravation of a chronic pancreatitis.

Material and methods. All patient were underwent esofagogastroduodenoscopy, ultrasonic research, research of pancreatic enzymes. The dynamics of painful abdominal syndrome was estimated by a technique of value judgment of expressiveness of a painful syndrome (on a 10-mark scale). Patients have divided into 3 groups, on expressiveness painful abdominal syndrome; 20 patients received omeprazole on 20 mg 2 times a day, 22 – pantoprazole in a daily dose of 80 mg, 25 – rabeprazole on 40 mg a day. Control group was consist of 10 practically healthy faces.

Results. Against the appointed therapy in all groups was marked the tendency to reduction of expressiveness painful abdominal syndrome was marked, considerable decrease in intensity painful abdominal a syndrome is noted in the second (up to 7.2 + 0.9 a point) and the third group (up to 6.4 + 0.7 a point) patients. The maintenance pancreatic amylase of blood prior to the beginning of treatment was authentically raised in all groups (144.8 + 10.2, 152.1 + 9.8 and 149.7 + 7.2 units/l accordingly) in comparison with control values (41.2 + 10.2 units/l, $p < 0.05$). After the leaded treatment in both groups the tendency to decrease in this indicator is noted. In comparison with reference values ($p < 0.05$) also have approached with control sizes (53.9 + 7.3, 48.8 + 7.5 and 42.8 + 11.3 units/l accordingly).

Conclusions. Thus, pantoprazole and rabeprazole render more expressed contra-selective marker effect, in comparison with omeprazole. The revealed dependence between degree of suppression gastric acid formation and expressiveness painful abdominal syndrome, level of a reduction of biochemical indicators of a pancreas allows inclusions pantoprazole and rabeprazole in the scheme of complex therapy of a chronic pancreatitis.

Khamrabaeva F.I. Place of application inhibitors of the proton pump in treatment of the chronic pancreatitis. In: *11th International Symposium of Gastroenterology, Saint Petersburg, Russia, 12–14 May 2016*. [online]. Available from URL: http://www.promedcs.eu/sites/default/files/abstractbook_2016.pdf

THE PATHOGENETIC APPROACH TO THERAPY OF CHRONIC PANCREATITIS OF THE BILIARNIC ETIOLOGY

F. I. KHAMRABAEVA

The Tashkent institute of postgraduate medical education, Tashkent; Uzbekistan

Research objective. To study efficiency microcapsulinic fermental preparation at illness of a chronic pancreatitis (CP) biliarnic etiologies.

Material and research methods. 30 patients with a chronic pancreatitis have been investigated. For diagnosis verification by all patient were carried out transabdominal ultrasonic research and a blood test on a pancreatic and hepatic profile.

The concentration of pancreatic I in a stool of patients was defined by a method immunoenzymatic analysis (ELISA).

Results. Research of indicators of the maintenance elastase in faecal matter before treatment has shown its tendency to decrease in both groups of patients: in the basic group the corresponding indicator has made 194.5 ± 27.3 mkg/g, and in comparison group – 201.6 ± 12.8 mkg/g (> 0.05). After the spent treatment indicators elastase in faecal matter have made 210.3 ± 17.2 mkg/g in the first group and 256.6 ± 18.2 mkg/g in the second group of patients. At the analysis of changes of laboratory indicators against therapy of Trizim microcaps 20 000 has been established that neutral fat is revealed in faecal matter at 16 patients, fat acids – at 13 which for 21 day of treatment have been eliminated at 65% of patients. At 19 patients, investigated activity decrease elastazy-1 in faecal matter was revealed. After the spent treatment with inclusion of Trizima microcaps 20 000 activity elastazy-1 at 85% of patients tended to normalization that correlates with disappearance painful abdominal a syndrome whereas in the first group sick receiving pancreatine considerable changes both to, and after course of treatment it was not observed.

Signs of the speeded up chair were normalized at 45% of the first and 75% of patients of the second group. Steathorea has disappeared at 40% of patients' control, against 89% of the basic group.

Conclusions. For pathogenesis treatment CP billiarnic with exocrine insufficiency pancreatic NA application microencapsulation fermental preparation of Trizim microcaps 20 000 is recommended to an aetiology.

Khamrabaeva F.I. The pathogenetic approach to therapy of chronic pancreatitis of the biliarnic etiology. In: *11th International Symposium of Gastroenterology, Saint Petersburg, Russia, 12–14 May 2016*. [online]. Available from URL: http://www.promedcs.eu/sites/default/files/abstractbook_2016.pdf

GILBERT'S SYNDROME AND CHANGES IN LIPOPROTEIN SPECTRUM

S. HLINSTAKOVA[1], I. OCADLIK[2], L. LUKAC[1], M. BUBAN[2]

1. Department of Internal Medicine, University Hospital Bratislava, 2. Railway Hospital, Bratislava

Introduction. The analysis of the serum bilirubin levels, lipid and lipoprotein parameters with the emphasis on the presence of atherogenic lipoproteins in the individuals with Gilbert's syndrome and control group.

Aims & Methods. Serum lipoproteins and their subfractions were examined using Lipoprint LDL System Quantimetrix, CA, USA. With this method, twelve lipoprotein classes and their sub-populations can be identified: very low density lipoproteins (VLDL), three subpopulations of intermediate density lipoproteins (IDL), seven subpopulations of low density lipoproteins (LDL) and high density lipoproteins (HDL). Subfractions LDL 3–7 represent highly atherogenic forms. HDL and LDL 1,2 subfractions represent non-atherogenic lipoproteins. Gilbert's syndrome (GS) was diagnosed using fragment analysis method. Based on the the presence of mutation in the promotor gene for UDP-glucuronosyltransferase volunteers were divided in two groups. Group 1 consisted of 40 probands confirmed to have Gilbert's syndrome. In group 2 – control group there were 60 subjects in whom the diagnosis of Gilbert's syndrome was excluded.

Results. In group 1 unconjugated bilirubin levels were significantly higher than in group 2 – 16.23 μmol/l vs. 4.83 μmol/l. In group 1 and group 2 LDL cholesterol levels were 2.66 and 2.92 mmol/l, respectively. LDL 1,2 subfractions levels were almost the same in both group – 1.72 mmol/l in group 1 and 1.74 mmol/l in group 2. Levels of atherogenic LDL 3–7 subfractions were significantly lower in the group 1 – 0.010 mmol/l compared to control group – 0.070 mmol/l. We also found higher HDL cholesterol levels in proband with GS – 1.32 mmol/l compared to 1.25 mmol/l in control group. Serum triglycerides levels were higher in control group (1.23 mmol/l) compared to subjects with GS (1.01 mml/l). In the group I, we found significantly negative correlation between serum unconjugated bilirubin levels and atherogenic LDL 3–7 nlipoproteins as well as between bilirubin and triglycerides level. Significant positive correlation was found between LDL 1,2 lipoproteins and serum bilirubin levels.

Conclusion. The presence of an atherogenic lipoprotein spectrum according to numerous studies is significantly lower in patients with Gilbert's syndrome. These results suggest that patients with Gilbert's syndrome (presented with higher serum levels of unconjugated bilirubin) could be protected against the development of atherosclerosis and its complications.

hlinstakova@gmail.com

Hlinstakova S., *et al*. Gilbert's syndrome and changes in lipoprotein spectrum. In: *11th International Symposium of Gastroenterology, Saint Petersburg, Russia, 12–14 May 2016*. [online].
Available from URL: http://www.promedcs.eu/sites/default/files/abstractbook_2016.pdf

THE METABOLISM OF LEPTIN IN TROPHOLOGICAL DISORDERS

M. A. LIVZAN, E. A. LYALYUKOVA, G. I. NECHAEVA, I. V. LAPTEVA, M. Y. ROZHKOVA

Omsk State Medical University, Omsk; Russian Federation

Trophological disorders as a malnutrition, overweight and obesity are associated with the risk of adverse events, including decompensation of chronic diseases, the development of infectious complications, fatalities. Leptin – a hormone produced by adipose tissue, is the main regulator of metabolic disorders.

Objective. To evaluate leptin and soluble leptin receptor in patients with various types of trophological disorders.

Materials and methods. In a cross-sectional comparative study cohort included 83 patients: 59 patients with symptoms of malnutrition of varying degrees (study group), 24 patients with normal trophological status (control group), 28 patients with excess body weight and obesity (control group). The median age was 20 (18.6–24.1) years. The groups were matched by sex and age. The criteria are not included in the study: the presence of acute or chronic disease at the time of entry into the study or history; conditions affecting the levels of leptin (recurrent thrombosis, diabetes, reproductive function, cardiovascular disease, pregnancy, lactation). Trophological status was assessed by anthropometric indicators: body mass index (BMI), the circumference of the shoulder muscles (CSM), the thickness of the skinfold above the triceps (TUZHST). The concentration of leptin was evaluated by enzyme immunoassay using the test system "LeptinELISAKit" (Canada), the concentration of soluble receptor – "HumanLeptinReceptor" (Czech Republic). Statistical analysis was performed using Statistica-8 packages. The correlation between the concentration of leptin and anthropometric measurements were assessed using Pearson's correlation test.

Results of the study. Malnourished patients had significantly lower values of leptin and higher concentrations of soluble leptin receptor as compared to the control group and comparison group (Table 1).

Table 1. Levels of leptin and soluble leptin receptor in the treatment groups

Indicator	Study group	Control Group	Comparing group	Statistically significant difference, p
BMI, kg/m^2	17.5 (16.7–18.4)	20.8 (19.7–24.4)	32.8 (29.0–35.4)	p = 0.002* p = 0.001**
Leptin, ng/ml	12.3 (11.5–14.7)	22.1 (20.0–13.5)	32.8 (31.1–34.9)	p = 0.006* p = 0.004**
Soluble receptors for leptin, ng/ml	34.3 (33.8–36.7)	30.9 (24.6–33.5)	18.8 (14.9–25.1)	p = 0.003* p = 0.02**

Note: * – difference from control group; ** – comparing group differences

Anthropometric indices patients correlated with serum leptin levels: BMI ($rs = 0.54$; $p < 0.01$), NBC ($rs = 0.63$; $p < 0.01$), TKZHST ($rs = 0.65$; $p < 0.01$), and soluble leptin receptor BMI ($rs = –0.34$; $p < 0.01$), NBC ($rs = –0.43$; $p < 0.01$), TKZHST ($rs = –0.67$; $p < 0.01$)

Conclusion. Concentrations of leptin and soluble leptin receptor correlated with changes trophological status of patients and can be used as serum markers of metabolic disorders. Evaluation of soluble leptin and its receptors will allow to individualize approaches to the management of patients at risk for metabolic disorders.

Lyalyukova E.A., *et al*. The metabolism of leptin in trophological disorders. In: *11th International Symposium of Gastroenterology, Saint Petersburg, Russia, 12–14 May 2016*. [online].
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THE HETEROGENEITY GERD BASED ON DATA OF THE 24-HOUR pH-IMPEDANCEMETRY

Nadezhda LISHCHUK

Northwestern State Medical University named after I. I. Mechnikov, Saint Petersburg; Russian Federation

Background. Gastroesophageal reflux disease (GERD) is the most common disease of the upper gastrointestinal tract. Proton pump inhibitors (PPIs) are the gold standard treatment for gastroesophageal reflux disease. However, in clinical practice, failure of PPIs occurs frequently, and may affect up to 30% of patients in a typical gastroenterology practice. In recent years it was found that most of these patients has "non-acid" reflux (weakly acidic or weakly alkaline). Whereas the clinical approach to patients with persistent acid reflux seems evident, the approach to patients with non-acid reflux is less evolved.

The aim of the study is: to explore the clinical and pathogenetic features of "non-acid" GERD, to evaluate the effect of monotherapy and combination therapy on the disease.

Methods. Multichannel impedance monitoring combined with pH monitoring detects and regists a non-acid reflux. Non-acid reflux disease can be diagnosed if symptoms correlate with these non-acid reflux episodes.

The study included 46 patients diagnosed with "non-acid" GERD. These patients were divided into 4 groups: the 1st gr. – patients with "weakly acidic" GER treated with monotherapy of rabeprazole 20 mg daily (12 patients), the 2nd gr. – patients with "weakly acidic" GER treated with combine therapy with rabeprazole 20 mg and itopride (15 patients), the 3rd gr. – patients with "alkaline" GER treated with monotherapy of ursodeoxycholic acid – 8 patients, and the 4th gr. – patients with "alkaline" GER treated with combine therapy with ursodeoxycholic acid and itopride (11 patients). The period of follow-up was 6 weeks. Clinical symptoms of the disease, the social and psychological status, the endoscopic and histological pictures, the infection of *H. pylori* was evaluated in dynamics. 24-hour pH impedansometry was conducted repeatedly after treatment.

Results. Analysis of the clinical picture of the disease showed that the severity of heartburn depends on the version of GERD. So heartburn that occurs daily and negatively affects the way of life (severe form) was observed in the group with "weak acid" GER at 46.4% and only 18.2% of the patients with "alkaline" GER ($p < 0.05$). At the same time, in group of patients with "alkaline" gastroesophageal reflux dyspepsia was significantly more frequently syndrome (82% and 63% respectively, $p < 0.05$). Duodenogastric reflux (DGR), diagnosed with 24-hour pH-impedance of the esophagus, was registered in 72.3% of patients with weakly acidic and weakly alkaline refluxes. This resonance was detected in all patients with "non-acidic" GERD and cholecystectomy in the anamnesis.

Patients with reflux-esophagitis had a more severe motor disorders than patients with non-erosive form of reflux disease, which was manifested by a large number of refluxes per day: (104 ± 92 refluxes vs. 82 ± 78, $p < 0.05$); higher percentage of time with $pH < 4$ in the esophagus: $2.3 \pm 1.7\%$ vs. $1.45 \pm 1.2\%$ ($p < 0.05$); a greater number of refluxes lasting more than 5 minutes: 4.7 ± 3.4 vs. 4.9 ± 7.0 ($p < 0.05$).

Conclusion. Treatment with different combine therapy (rabeprazole + itopride, itopride + UDCA) leads to the acceleration in the reduction of clinical and endoscopic picture of GERD. In repeated pH-impedancemetry was found that using of PPIs with prokinetic for weakly acidic refluxes and prokinetic with UDCA for weakly alkaline refluxes reliably reduce the total number of GER, the total percentage reflux time and the number of proximal refluxes. It should be noted that positive dynamics was observed not only in groups of combine therapy, but in patients who were treated only by UDCA.

lishchuk.nadezhda@mail.ru; Phone: +79218905839

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