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AAIM: GI Workshop – Follow Up to Case Studies

Non-alcoholic Fatty Liver Disease
Ulcerative Colitis
Crohn’s Disease

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VP and Medical Director, RGA Global

October 2015
Non-alcoholic Fatty Liver Disease (NAFLD)

Core Principles
NAFLD – Non-alcoholic fatty liver disease

Definitions

- **NAFLD**
  - Evidence of hepatic steatosis, either by imaging or histology with > 5% steatotic hepatocytes
  - No identified causes for secondary hepatic fat accumulation

- **Causes of secondary hepatic fat accumulation**
  - Excess EtOH, Hep C (genotype 3), Wilson’s disease, lipodystrophy, starvation, parenteral nutrition, abetalipoproteinemia, medications, (e.g. amiodarone)
  - Excess EtOH defined as: > 20 gm/d female and >30 gm/d male

- **NAFLD is a spectrum (steatosis → cirrhosis) of disease but primarily divided into:**
  - Non-alcoholic fatty liver (NAFL) – no histological evidence of hepatocellular injury
  - Non-alcoholic steatohepatitis (NASH) – histological evidence of inflammation, hepatocellular ballooning (injury) with or without fibrosis – indistinguishable from alcoholic steatohepatitis
NAFLD – Epidemiology and Risk Factors

- **Prevalence**
  - Japan: 31-86/1,000 person-years
  - UK: 29/100,000
  - Dallas Heart Study (using MR spectroscopy): 31% of gen pop
  - Worldwide estimates of 6.3-33% with median of 20%
  - NASH estimates lower at 3-5%

- **Risk Factors**
  - Obesity: With BMI > 30 the prevalence is > 60%, prevalence increases to > 90% with BMI > 39!
  - DM-2: up to 69% may have NAFLD
  - Hyperlipidemia: 50% of dyslipidemia clinic attendees have NAFLD
  - NAFLD prevalence increases with age
  - Males > Females
NAFLD – Lab Findings

- **Liver Enzymes**
  - ALT and AST may be elevated up to 5x ULN
  - AST/ALT ratio usually < 1
  - Alk phos and GGT may also be elevated
  - Degree of liver enzyme elevations *does not* correlate with clinical inflammation or fibrosis
  - Ferritin > 1.5x ULN may correlate with higher likelihood of NASH being present

- **Imaging**
  - Liver US is 82-89% sensitive and 93% specific for identifying fatty infiltrate
  - CT no more sensitive than US, but can identify other pathology
  - Imaging *cannot* distinguish steatosis from steatohepatitis
NAFLD – Grade and Stage of Liver Biopsy

- **Grade**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1 – mild</td>
<td>Steatosis in up to 66% of hepatocytes, occasional ballooned hepatocyte, scattered neutrophils +/- lymphocytes in hepatic lobules, no or mild portal inflammation</td>
</tr>
<tr>
<td>Grade 2 – moderate</td>
<td>Steatosis of any degree, some ballooned hepatocytes and neutrophils, pericentral fibrosis may be present, mild to moderate portal and lobular inflammation</td>
</tr>
<tr>
<td>Grade 3 – severe</td>
<td>Diffuse lobular steatosis, widespread ballooning and lobular inflammation with pericentral vein fibrosis, mild to moderate portal inflammation</td>
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- **Stage – degree of fibrosis**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No fibrosis</td>
</tr>
<tr>
<td>1</td>
<td>Zone 3 perisinusoidal fibrosis only</td>
</tr>
<tr>
<td>2</td>
<td>Zone 3 plus portal/periportal fibrosis</td>
</tr>
<tr>
<td>3</td>
<td>As above with bridging fibrosis</td>
</tr>
<tr>
<td>4</td>
<td>Cirrhosis</td>
</tr>
</tbody>
</table>
NAFLD – Morbidity and Mortality Risk

Multiple studies – somewhat conflicting results

▪ Issues
  • Epidemiologic studies are often based on biochemical and imaging studies and not biopsy
  • Difficult to control for co-variates which may also increase risk of death and CV outcomes
  • NAFLD may only be a “serious condition” in a sub-group of individuals with NAFLD – the challenge is to identify those individuals.

▪ Morbidity
  • Large meta-analysis found OR of 1.50 for CV events when other risks controlled.

▪ Mortality
  • Variable results, but increased MRs in the range of 1.34-1.69, mostly due to CV disease.
NAFLD – Other Points

- Risk factors of progression to advanced fibrosis:
  - Presence of inflammation on biopsy increases risk 2.5x.
  - Older age, DM, AST and ALT > 2x ULN, ballooning degeneration, Mallory hyaline or fibrosis on biopsy, and BMI > 28.

- NASH is 3rd most common indication for liver transplant in the U.S. – may become the most common indication in the next 10-20 years.

- Risk of hepatocellular carcinoma in individuals with cirrhosis due to NAFLD may be lower than in those with cirrhosis due to hepatitis C.

- Therapeutic interventions to treat or reverse NAFLD:
  - Effective - Weight loss, bariatric surgery, TZDs, vitamin E (NASH), obeticholic acid
  - Not effective – metformin, ursodeoxycholic acid, omega-3s
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Ulcerative Colitis – Mortality

- SMRs range from 0.7 – 1.4 depending on study
- Mortality highest in first few years after diagnosis and in those with extensive disease
- Mortality rates have decreased over time
Ulcerative Colitis – Extra-intestinal manifestations

- 25% of patients develop extra-intestinal manifestations over course of their disease
  - Arthritis, ankylosing spondylitis (AS), scleritis, iritis, erythema nodosum, pyoderma gangrenosum, primary sclerosing cholangitis (PSC), autoimmune hepatitis, thromboembolism

- Primary sclerosing cholangitis occurs in 3-7% of those with UC and approximately 2/3 of those with PSC will develop UC
  - Higher risk of PSC in men and those with pancolitis
  - Suspect possible PSC in individuals with UC and elevated alkaline phosphatase/GGT

- Most extra-intestinal manifestations parallel course of colonic disease activity except for PSC and AS
Ulcerative Colitis – Colorectal (CRC) cancer risk

- Two main risk factors for the development of CRC
  - Duration of disease: Increased risk > 10 years
  - Extent of disease: Pancolitis (or > 50% of colon)  

- Pancolitis CRC risk
  - 5-10% after 20 years, 12-20% after 30 years, 30% after 35 years (varies based on study)

- Left-sided colitis CRC risk
  - Risk increases later than pancolitis: 15-20 years after diagnosis

- Ulcerative proctitis and proctosigmoiditis CRC risk
  - No increase risk of CRC

- Individuals with both UC and PSC have even higher risk of CRC than those with UC alone

Standardized incidence ratio = 7.0
Ulcerative Colitis – Surveillance

- Standardized frequency of colonoscopic surveillance not established

- Various societies with different recommendations, but in general:
  - Start surveillance after 8-10 years of disease in those with pancolitis and after 15 years in those with left-sided colitis
  - Repeat every 1-5 years depending on deemed risk

- Dysplasia on random colon biopsies

<table>
<thead>
<tr>
<th>Low Grade Dysplasia</th>
<th>High-Grade Dysplasia</th>
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<tbody>
<tr>
<td>19% have CRC at immediate colectomy</td>
<td>40% have CRC at immediate colectomy</td>
</tr>
<tr>
<td>34% have CRC at colectomy in 1 year</td>
<td>Presence of high-grade dysplasia should lead to immediate colectomy</td>
</tr>
<tr>
<td>Can regress spontaneously</td>
<td></td>
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Crohn’s Disease - Mortality

- Varying results of studies
- Large study from 2007 determined overall SMR of 1.29 which was unchanged from the 1970s
- MRs decreased with increasing age
Crohn’s disease – CRC cancer risk and surveillance

- Risk of CRC is likely similar to risk in UC
- RR of CRC higher in Crohn’s individuals primarily with colonic disease and those diagnosed under age 30 years
- Crohn’s may increase risk of small bowel cancer
- Most societies recommend the same colonoscopic surveillance protocols for Crohn’s as for UC, although the supportive data is less definitive.
Crohn’s disease – other

- Risk of PSC is slightly lower than with UC – approximately 3.5%
References


- www.uptodate.com Epidemiology, clinical features, and diagnosis of nonalcoholic fatty liver disease in adults

- www.uptodate.com Natural history and management of nonalcoholic fatty liver disease in adults
References

- [www.uptodate.com](http://www.uptodate.com) Colorectal cancer surveillance in inflammatory bowel disease