EIGHT different award types; INCREASED Junior Faculty FUNDING; NEW Health Equity Research Award; Med Resident and Student Awards

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Grant System Opens: September 7, 2021
Deadline: December 3, 2021

Read the Grant Flyer, FAQs, or visit the webpage for the full RFAs.

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EIGHT different award types; NEW Health Equity Research Award; Bridge Funding; GIQuIC Research funding; Med Resident and Student Awards

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Participating in the Webinar

All attendees will be muted and will remain in Listen Only Mode.

Type your questions here so that the moderator can see them. Not all questions will be answered but we will get to as many as possible.
How to Receive CME and MOC Points

LIVE VIRTUAL GRAND ROUNDS WEBINAR
ACG will send a link to a CME & MOC evaluation to all attendees on the live webinar.

ABIM Board Certified physicians need to complete their MOC activities by December 31, 2021 in order for the MOC points to count toward any MOC requirements that are due by the end of the year. No MOC credit may be awarded after March 1, 2022 for this activity.

MOC QUESTION

If you plan to claim MOC Points for this activity, you will be asked to: Please list specific changes you will make in your practice as a result of the information you received from this activity.

Include specific strategies or changes that you plan to implement. THESE ANSWERS WILL BE REVIEWED.
ACG Virtual Grand Rounds
Join us for upcoming Virtual Grand Rounds!

Week 43, 2021
PSC and Transplantation
Fredric D. Gordon, MD
November 11, 2021 at Noon Eastern

Week 44, 2021
Disparities in Access and Outcomes for Common GI Conditions
Geoffrey C. Nguyen, MD, PhD, FRCPC
December 2, 2021 at Noon Eastern

Visit gi.org/ACGVGR to Register

Disclosures:

Speaker:
Colin W. Howden, MD, FACG
Consultant: RedHill Biopharma, Phathom Pharmaceuticals, Allakos, Clexio, Ironwood; Speakers’ Bureau: Alnylam, RedHill Biopharma, Alfasigma; Stock Ownership: Antibe Therapeutics

Moderator:
Rhonda F. Souza, MD
Consultant: Ironwood Pharmaceuticals, Cernostics, Phathom Pharmaceuticals, IsoThrive, CDx Diagnostics, and AstraZeneca; Research Support: Phathom Pharmaceuticals, Sanofi

*All of the relevant financial relationships listed for these individuals have been mitigated
The American College of Gastroenterology acknowledges educational grant support for this Virtual Grand Rounds webinar from:

RedHill Biopharma, Inc.

H. pylori: What it Does and Doesn’t Cause - and How Best to Treat it

COLIN W. HOWDEN MD, FACG
PROFESSOR EMERITUS
UNIVERSITY OF TENNESSEE COLLEGE OF MEDICINE
Natural history of *H. pylori* infection


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Sir William Osler

*Cancer of the Stomach*
*A Clinical Study*

(Published 1900)
ACG clinical guideline 2017: Epidemiology

- *H. pylori* infection is chronic and is usually acquired in childhood. The exact means of acquisition is not always clear.
  - The incidence and prevalence of *H. pylori* infection are generally higher among people born outside North America than among people born here.
  - Within North America, the prevalence of the infection is higher in certain racial and ethnic groups, the socially disadvantaged, and people who have immigrated to North America.

Chey et al, Am J Gastroenterol 2017; 112: 212

14

ACG clinical guideline 2007

Test for – and treat – *H. pylori* infection

- Active peptic ulcer disease (PUD)
- Confirmed history of PUD
- Low grade gastric MALT lymphoma
- Post-resection of early gastric cancer

Chey and Wong, Am J Gastroenterol 2007; 102: 1808

15
### ACG clinical guideline 2017

**Additional indications to test for – and treat – H. pylori infection**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Strength of recommendation</th>
<th>Quality of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uninvestigated dyspepsia (Age &lt; 50; no alarm features)</td>
<td>Conditional</td>
<td>High (efficacy) Low (age)</td>
</tr>
<tr>
<td>Long-term, low-dose aspirin</td>
<td>Conditional</td>
<td>Moderate</td>
</tr>
<tr>
<td>Prior to chronic NSAID therapy</td>
<td>Strong</td>
<td>Moderate</td>
</tr>
<tr>
<td>Established on NSAID therapy</td>
<td>Conditional</td>
<td>Low</td>
</tr>
<tr>
<td>Unexplained iron deficiency</td>
<td>Conditional</td>
<td>Low</td>
</tr>
<tr>
<td>ITP</td>
<td>Conditional</td>
<td>Very low</td>
</tr>
</tbody>
</table>

Chey et al, Am J Gastroenterol 2017; 112: 212

---

### Ulcer recurrence rates according to treatment for H. pylori infection

Meta-analysis
- DU: 26 trials / 2434 patients
- GU: 9 trials / 774 patients

**DU:** NNT = 2
**GU:** NNT = 3

*Ford et al, Am J Gastroenterol 2004; 99: 1833*
**H. pylori and gastric cancer**

Meta-analysis of 7 RCTs (8323 healthy / H. pylori-positive)
RCTs conducted in Asia
Randomized to active treatment v. placebo / no treatment
Treatment of infection led to
- Reduced incidence of gastric cancer \( RR \ 0.54; \ NNT \ 72 \)
- Reduced mortality from gastric cancer \( RR \ 0.61; \ NNT \ 135 \)
- No change in all-cause mortality

*Ford et al, Gut 2020; 69: 2113*

**H. pylori and gastric cancer: US VA database**

Retrospective cohort study of >370,000 veterans
Around 10% infected (test of active infection)
- Mean follow-up 7.4 y; around 1 in 200 developed gastric cancer

Not all infected patients were treated!
Successful, confirmed eradication associated with 76% reduction in risk of gastric cancer

*Kumar et al, Gastroenterology 2020; 158: 527
Howden, Gastroenterology 2020; 158: 466*
H. pylori and functional dyspepsia

Should biopsy normal-appearing gastric mucosa in patients having endoscopy for dyspepsia
A proportion will be H. pylori-positive
A proportion of those will have sustained symptom improvement after eradication
 ◦ Unfortunately, most won’t …

Concept of H. pylori-related dyspepsia as a subset of functional dyspepsia

Yang et al, Gastroenterology 2015; 148: 1082

H. pylori and functional dyspepsia (ACG and CAG clinical guideline)

“We recommend functional dyspepsia patients that are H. pylori-positive should be prescribed therapy to treat the infection”

22 RCTs (4896 FD patients) comparing eradication therapy with placebo antibiotics; follow-up 3 – 12 months

Statistically significant benefit of H. pylori eradication
 ◦ Dyspepsia persisted in 68% of treated patients v. 76% of controls
 ◦ RR of dyspepsia remaining = 0.91 (95% CI 0.88 – 0.94)
 ◦ NNT = 12.5 (95% CI 10 to 20)

Moayyedi et al, Am J Gastroenterol 2017; 112: 988
### Proposed extra-intestinal conditions linked to *H. pylori* infection

<table>
<thead>
<tr>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acromegaly</td>
</tr>
<tr>
<td>Anorexia of ageing</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
</tr>
<tr>
<td>Coronary heart disease</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Henoch-Schonlein purpura</td>
</tr>
<tr>
<td>Hepatic encephalopathy</td>
</tr>
<tr>
<td>Hyperemesis gravidarum</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Iron deficiency</td>
</tr>
<tr>
<td>ITP</td>
</tr>
<tr>
<td>Parkinson's disease</td>
</tr>
<tr>
<td>Psoriasis</td>
</tr>
<tr>
<td>Raynaud's phenomenon</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>Rosacea</td>
</tr>
<tr>
<td>Scleroderma</td>
</tr>
<tr>
<td>Sudden infant death syndrome</td>
</tr>
<tr>
<td>Urticaria</td>
</tr>
</tbody>
</table>

*Leontiadis et al, Arch Intern Med 1999; 159: 925*
**Extra-intestinal associations of *H. pylori***

Mostly based on uncontrolled observations

Usually no clear biological rationale

Treatment trials often uncontrolled

Two possible exceptions

- Iron deficiency with or without anemia
- Idiopathic thrombocytopenic purpura

Leontiadis et al, Arch Intern Med 1999; 159: 925

---

**H. pylori and ITP**

696 adult patients with ITP treated for *H. pylori* infection

- 43% had complete response (> 100 x 10^9/L)
- 50% had partial response (> 30 x 10^9/L and doubling of baseline count)

American Society of Hematology

- “screening for *H. pylori* infection should be considered in adults with ITP in whom eradication therapy would be used if testing is positive”

1. Stasi et al, Blood 2009; 113: 1231
Treatment of *H. pylori* infection: General considerations

- Require a positive test of active infection
- Offer treatment to all who test positive
- Explain the treatment, possible side effects *etc*

Choice of treatment?
- Availability of antimicrobial sensitivity testing?
- History of macrolide / quinolone use?
- True penicillin allergy?

Re-test after treatment

---

Treatment of *H. pylori* infection: Choosing a treatment regimen

Avoid clarithromycin if ¹
- History of macrolide use
- No antimicrobial sensitivity testing available
- Local resistance rate > 15% or unknown

Allergist referral if “penicillin allergy” in absence of anaphylaxis

Current regimens that do not require sensitivity testing ²
- Bi-based quadruple therapy
- PPI-rifabutin-amoxicillin

---

1. Chey et al, Am J Gastroenterol 2017; 112: 212
2. Howden and Graham, Am J Gastroenterol 2021; 116: 1
Antimicrobial resistance by \textit{H. pylori}: (Re)-stating the obvious

1. \textit{H. pylori} infection is usually acquired in childhood
2. \textit{H. pylori} lives in the stomach
3. \textit{H. pylori} has been exposed to every antibiotic consumed by mouth since childhood
## Antimicrobial resistance – US

<table>
<thead>
<tr>
<th>Years of study</th>
<th>CLA</th>
<th>MET</th>
<th>AMOX</th>
<th>TET</th>
<th>LEVO</th>
<th>RIF</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Houston VA</td>
<td>16</td>
<td>20</td>
<td>0</td>
<td>1</td>
<td>31</td>
<td>N/A</td>
</tr>
<tr>
<td>2 Alaska</td>
<td>30</td>
<td>43</td>
<td>2</td>
<td>&lt; 1</td>
<td>14</td>
<td>N/A</td>
</tr>
<tr>
<td>3 Delaware valley</td>
<td>43</td>
<td>42</td>
<td>N/A</td>
<td>N/A</td>
<td>69</td>
<td>N/A</td>
</tr>
<tr>
<td>4 US RCT</td>
<td>17</td>
<td>44</td>
<td>6</td>
<td>3</td>
<td>58</td>
<td>0</td>
</tr>
<tr>
<td>5 Rhode Island</td>
<td>30</td>
<td>33</td>
<td>1</td>
<td>&lt; 1</td>
<td>30</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>6 US RCT</td>
<td>22</td>
<td>65</td>
<td>2</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

4. Hulten et al, Gastroenterology 2021; 161: 342
5. Argueta et al, Gastroenterology 2021; 160: 2181

## Antimicrobial resistance – Europe

<table>
<thead>
<tr>
<th>Resistance (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clarithromycin 21.4</td>
</tr>
<tr>
<td>Levofloxacin 15.8</td>
</tr>
<tr>
<td>Metronidazole 38.9</td>
</tr>
<tr>
<td>Amoxicillin 0.2</td>
</tr>
<tr>
<td>Tetracycline 0</td>
</tr>
<tr>
<td>Rifampicin 0.9</td>
</tr>
</tbody>
</table>

Megraud et al, Gut 2021; 70: 1815

1211 adults, 2008 - 2017
24 centers in 18 European countries
Prior macrolide use → CLA resistance
(P = 0.0003)
Prior quinolone use → LEVO resistance
(P = 0.0002)
Rapid Prediction of *H. pylori* Antibiotic Resistance Using Next Generation Sequencing of Stool Samples Compared to Gastric Biopsies

Steven F. Moss*, Amporn Atsawarungruangkit*, Long P. Dang^, David Chua#, Yi Zhou@, Zhao Z. Chong®, Hongjun Zhang®, David Y. Graham†.

* Brown University, Providence, RI. ^ Fountain Valley Hospital, Fountain Valley CA. # Summit Digestive, Chicago, IL. @ American Molecular Labs, Vernon Hills, IL. † Baylor College of Medicine, Houston, TX

Introduction

• *H. pylori* eradication rates have declined largely due to rising antimicrobial resistance worldwide.
• Rapid, accurate, reliable antibiotic resistance testing is needed.
• Culture-based susceptibility testing requires endoscopy to obtain gastric biopsies, with resultant inconvenience and costs. Added to this, complex sample processing means it is not commonly performed in many GI practices.
• Molecular resistance testing of gastric biopsies using next generation sequencing (NGS) has become available recently, yielding results similar to those of culture-based methods, with more convenience to clinicians.
• Whether reliable resistance testing by NGS is possible from stool samples remains unclear.

• Identical profiles for stool and biopsy samples in 65/71 patients (91.5%).
• In 6 cases there was mismatch between gastric and stool results
  • in 4 cases this was due to 1 antibiotic-associated mutation difference
    (In 2 cases: 1 more mutation in stool; In 2 cases: 1 more mutation in gastric)
  • in 1 case: 2 mutations in gastric sample, none in stool
  • In 1 case: 3 mutations in gastric sample, only 1 of these in stool

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Gene evaluated</th>
<th>Resistance Associated Mutations (N, %)</th>
<th>Agreement between tests (κ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clarithromycin</td>
<td>23S rRNA</td>
<td>39 (54.9%) 39 (54.9%)</td>
<td>0.94 (95% CI: 0.86-1.00)</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>gyr A</td>
<td>23 (32.4%) 20 (28.2%)</td>
<td>0.90 (95% CI: 0.79-1.00)</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>rdxA</td>
<td>23 (32.4%) 21 (29.6%)</td>
<td>0.89 (95% CI: 0.74-0.99)</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>16s rRNA</td>
<td>7 (9.9%) 7 (9.9%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>pbp1</td>
<td>4 (6%) 4 (6%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Rifabutin</td>
<td>rpoB</td>
<td>0 (0%) 0 (0%)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Conclusions
• Resistance is a major cause of treatment failure. We confirm that clarithromycin, metronidazole, and levofloxacin triple therapies should only be used in susceptibility-based therapy.
• Resistance to amoxicillin and tetracycline may be increasing.
• Profiling *H. pylori* antibiotic resistance by NGS from stool samples provides rapid results highly comparable to those obtained from gastric biopsies.
• Using NGS to determine *H. pylori* antibiotic resistance using stool obviates the cost, inconvenience and risks of endoscopy for resistance profiling.
### Success rates with different regimens – U.S. “real world” data

<table>
<thead>
<tr>
<th>Regimen</th>
<th>N</th>
<th>Cure rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bi-based quadruple (tetracycline), 14 days</td>
<td>585</td>
<td>87%</td>
</tr>
<tr>
<td>Bi-based quadruple (tetracycline), 10 days</td>
<td>135</td>
<td>77%</td>
</tr>
<tr>
<td>PPI-clarithromycin-amoxicillin, 14 days</td>
<td>161</td>
<td>79%</td>
</tr>
<tr>
<td>PPI-clarithromycin-amoxicillin, 10 days</td>
<td>101</td>
<td>67%</td>
</tr>
<tr>
<td>Bi-based quadruple (doxycycline), 14 days</td>
<td>48</td>
<td>70%</td>
</tr>
<tr>
<td>Bi-based quadruple (doxycycline), 10 days</td>
<td>16</td>
<td>67%</td>
</tr>
</tbody>
</table>

*Alsamman et al, Dig Dis Sci 2019; 64: 2893*

### Success rates with different regimens – U.S. “real world” data

<table>
<thead>
<tr>
<th>Regimen</th>
<th>N</th>
<th>Cure rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>187</td>
<td>75.4</td>
</tr>
<tr>
<td>Bi-based quadruple (tetracycline)</td>
<td>79</td>
<td>89.9</td>
</tr>
<tr>
<td>Bi-based quadruple (doxycycline)</td>
<td>18</td>
<td>83.3</td>
</tr>
<tr>
<td>Non Bi-based quadruple / concomitant</td>
<td>4</td>
<td>75.0</td>
</tr>
<tr>
<td>Clarithromycin-based triple</td>
<td>62</td>
<td>58.1</td>
</tr>
</tbody>
</table>

*(91.4% of patients were treated for 14 days)*

*Argueta et al, Gastroenterology 2021; 160: 2181*
Network meta-analysis
Comparative effectiveness of different regimens

68 RCTs; 22,975 patients; 8 different first-line regimens
Vonoprazan-based triple therapy had best results
Standard triple therapy was the least efficacious

Overall cure rates
- Vonoprazan-based triple therapy: 91.4% (all trials from East Asia)
- Bi-based quadruple therapy: 81.3% (81.2% in west)
- PPI-clarithromycin-amoxicillin: 75.7% (67.8% in west)

Rokkas et al, Gastroenterology 2021; 161: 495

Rifabutin-based triple regimen (RHB-105) for H. pylori infection

Rifabutin-based triple regimen (RHB-105) for *H. pylori* infection

Approved by FDA November 2019 for “… treatment of *H. pylori* infection in adults”

Total daily doses
- Omeprazole 120 mg
- Amoxicillin 3000 mg
- Rifabutin 150 mg

14-day regimen; 4 capsules *t.i.d.*

https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/213004lbl.pdf

Life and death of *H. pylori*:
Why elevating pH helps in eradication

Scott et al, Gut 1998; 43: S56
Potassium-competitive acid blockers (P-CABs)

Licensed in some Asian and South American countries

Faster onset of action and more profound control of acid secretion than PPIs

Examples include revaprazan, vonoprazan, tegoprazan and fexuprazan

Phase 3 trials of vonoprazan in US and Europe

- H. pylori infection
- erosive esophagitis

Abdel-Aziz et al, Aliment Pharmacol Ther 2021; 53: 794

Comparison of vonoprazan and esomeprazole on 24-hour intragastric pH (Japan)

Abdel-Aziz et al, Aliment Pharmacol Ther 2021; 53: 794

Sakurai et al, Aliment Pharmacol Ther 2015; 42: 719
HP-301: Efficacy and safety of vonoprazan compared to lansoprazole in participants with *H. pylori* infection (NCT04167670)

Randomized, blinded, controlled comparison of:
- Vonoprazan 20 mg *bid*, amoxicillin 1 g *tid*
- Vonoprazan 20 mg *bid*, amoxicillin 1 g *bid*, clarithromycin 500 mg *bid*
- Lansoprazole 30 mg *bid*, amoxicillin 1 g *bid*, clarithromycin 500 mg *bid*

Treatment for 14 days
Success determined by $^{13}$C-UBT 4 weeks after end of therapy

https://clinicaltrials.gov/ct2/show/NCT04167670

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Second-line / salvage treatment: General principles

- Confirm that infection has not been eradicated
  - UBT / fecal antigen test – NOT SEROLOGY
- Do not re-use clarithromycin or levofloxacin
- Assess patient adherence to treatment
- Emphasize importance of completing the course
- Discuss potential / expected adverse effects
- Treat for 14 days

Failure after clarithromycin-based triple therapy (PAC or PMC) or concomitant therapy (PAMC)

- PBMT
- If fails
- True penicillin allergy? (Allergy testing, if appropriate)

Failure after PBMT

AGA, American Gastroenterological Association; PAC, proton pump inhibitor, amoxicillin, clarithromycin; PAMC, proton pump inhibitor, metronidazole, amoxicillin, clarithromycin; PBMT, proton pump inhibitor, bismuth, metronidazole, tetracycline; PMC, proton pump inhibitor, metronidazole, clarithromycin.

Failure after clarithromycin-based triple therapy (PAC or PMC) or concomitant therapy (PAMC)

PBMT

If fails

True penicillin allergy? (Allergy testing, if appropriate)

NO

Failure after PBMT

Population levofloxacin resistance < 15%, or known sensitive strain

If fails

Failure after PBMT

PAR

PAL or PBLA

PAL, proton pump inhibitor, amoxicillin, levofloxacin; PAR, proton pump inhibitor, amoxicillin, rifabutin; PBLA, proton pump inhibitor, bismuth, levofloxacin, amoxicillin.

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True penicillin allergy? (Allergy testing, if appropriate)

Options after sensitivity testing include PAR, high-dose dual PA, levofloxacin quad therapy (PBLT or PBLM), or repeat PBMT.

Failure after clarithromycin-based triple therapy (PAC or PMC) or concomitant therapy (PAMC)

Population levofloxacin resistance < 15%, or known sensitive strain

Population levofloxacin resistance ≥ 15%, or known resistant strain

Failure after PBMT

PBCT, proton pump inhibitor, bismuth, clarithromycin, tetracycline; PBLT, proton pump inhibitor, bismuth, levofloxacin, tetracycline; PBLM, proton pump inhibitor, bismuth, levofloxacin, metronidazole.

True penicillin allergy? (Allergy testing, if appropriate)
Summary

Chronic infection with serious consequences
Test of active infection prior to treatment
Choose treatment regimen carefully
  - Patient’s antibiotic history is crucial
  - Avoid clarithromycin unless known susceptibility
  - Discuss importance of adherence, possible side effects
Re-test at least 4 weeks after completion of treatment
  - UBT, fecal antigen test, (endoscopy)

Questions?

Speaker:
Colin W. Howden, MD, FACG

Moderator:
Rhonda F. Souza, MD
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ACG Women in GI Circle

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