Interpreting the DRG Helicobacter Plus Profile (HPP) Report

Bernadette M. Mandes Wildemore, MD
Medical and Laboratory Director
DRG Laboratory
This test was developed and its performance characteristics determined by DRG Laboratory.

Diagnosis and treatment are the responsibility of the ordering physician.
Helicobacter Plus Profile (HPP)

- Performed on biopsy samples submitted to lab
- Evaluates for molecular evidence of
  - *Helicobacter pylori* (*H. pylori*)
  - *H. pylori* virulence factor *cagA*
  - *H. pylori* virulence factor *iceA*
  - *H. pylori* virulence factor *oipA*
  - *H. pylori* virulence factor *vacA*
  - *H. pylori* clarithromycin susceptibility
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- *Helicobacter pylori (H. pylori):*
  - Result: Negative or Positive
  - This is a quantitative value that informs the clinician if the *H. pylori* bacterium is (or has been) present
    - PLEASE NOTE: This value is only evidence that the bacterium has been present at some point during the past few years. The molecular evidence of the organism may remain even if the bacterium itself has been eradicated, either by the patient’s own immune system OR by exogenous therapy (antibiotics or the like). It is NOT evidence of an active or current infection
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- If the clinician chooses to use the HPP assay in isolation, the clinician must work in concert with the laboratory for the best patient outcome.

- The clinician (gastroenterologist) MUST be vigilant to perform regular follow-up endoscopies to determine for the development of pre-neoplastic changes.
Endoscopic photos of *H. pylori*
Histologic photos of *H. pylori*

H & E stain (note PMNs)  
Warthin-Starry stain
Interpreting the HPP report

- *H. pylori* virulence factor *cagA*: Negative or **positive**
- *H. pylori* virulence factor *iceA*: Negative or **positive**
- *H. pylori* virulence factor *oipA*: Negative or **positive**
- *H. pylori* virulence factor *vacA*: Negative or **positive**

- If any of the above virulence factors are **positive**, this indicates that the patient is at increased risk for the development of significant consequences of HP infection.
- Furthermore, note that virulence factors may be present, even in the absence of HP infection.
What are the virulence factors?

- Several factors have been implicated as virulence determinants of HP, and associated with advanced GI disease

  - **CagA protein** (encoded by *cagA* gene): Found in 50-60% HP of Western patients
    - Induces inflammation via IL-8 secretion and NF-kB activation
    - Member of *cag* pathogenicity island → CagA protein translocated in GI epithelial cells and tyrosine phosphorylated → induces growth factor like phenotypes in host cell

Ogura 2000
What are the virulence factors, cont.?

- Several factors have been implicated as virulence determinants of HP, and associated with advanced GI disease.

  - **Ice protein** (encoded by *iceA* gene)
    - The function of this gene is not yet fully elucidated.
    - Currently thought to be upregulated when HP contacts GI epithelium.
    - Strongly believed to be a marker for peptic ulcer disease (PUD).

Mousavi 2014
What are the virulence factors, cont.?

Several factors have been implicated as virulence determinants of HP, and associated with advanced GI disease.

- **Oip A protein** (encoded by oipA gene)
  - Upregulated when HP contacts GI epithelium
  - Induces IL-8 secretion
  - Associated with clinically significant presentation of PUD

Mousavi 2014
What are the virulence factors, cont.?

- Several factors have been implicated as **virulence** determinants of HP, and associated with advanced GI disease
  - **VacA protein** (encoded by vacA gene)
    - Results in cytotoxic vacuolation
    - Vacuolation more frequently associated with **severe gastritis** and **metaplasia**

Ogura 2000
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- Virulence factors give **additional** information to the treating physician regarding the potential for the development of gastric cancer (GC)
  
  - The development of GC involves the interplay among three important factors
    
    - The agent (generally, *H. pylori*) and its **pathogenicity**
    
    - Host (patient) characteristics
    
    - Environment
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- Regarding *H. pylori*, some studies show that eliminating the infection may reduce the incidence of GC in patients without pre-neoplastic lesions.

- If pre-neoplastic lesions are present, elimination of the *H. pylori* infection may reduce the incidence of GC.

- In patients with a previously resected gastric adenocarcinoma (GA), *H. pylori* eradication may decrease the recurrence of metachronous GA.
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- Again, if the practice chooses to use the HPP in isolation, alertness is even more imperative on the part of the physician to perform regular endoscopies to carefully evaluate for the endoscopic evidence of pre-neoplastic mucosal changes.

- Pre-neoplastic lesions examples
  1. Gastric mucosal atrophy
  2. Intestinal metaplasia
Pre-neoplastic lesions by endoscopy

- Gastric atrophy
- Intestinal metaplasia
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- Intestinal vs. diffuse adenocarcinoma GC types
  - **Intestinal GC** (well-differentiated) believed to be preceded by sequence of precursor lesions
    - Chronic inflammation of gastric mucosa (usually in older patients)
      - Atrophic gastritis
        - Intestinal metaplasia
          - Dysplasia
            - Gastric cancer

Takenda 2007
Interpreting the HPP report

- Intestinal vs. diffuse GC types
  - Intestinal type GC (60-70%)
    - Older age, > incidence in males
    - Environmental causes
    - Discrete, defined tumor
    - *H. pylori* important
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- Intestinal vs. diffuse GC types
  - Diffuse GC (poorly-differentiated) (30-40%)
    - Associated issues include
      - Familial distribution, usually younger patients
      - Chronic inflammation of gastric mucosa (particularly in the cardia)
        - Mutation of CDH-1 (e-cadherin) gene
        - Downstream activation leads to further proliferation
      - Cancer formation
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- Virulence factors (VF)
  - The high level of genetic diversity may play a critical role in the adaptation of the host gastric mucosa with VF
  - VF may also contribute to the ultimate clinical outcome of the patient (although research is ongoing)
  - Nevertheless, the virulence factors have been associated with increased virulence of the infecting organism

Pacheco (2008), Roesler (2011)
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- Results suggest that HP eradication improves neutrophil (polymorphonuclear cell, or PMN) infiltration and intestinal metaplasia in the gastric mucosa → inhibiting new, early stage gastric carcinoma
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- Research is ongoing; however
  - The risk of GA is related to severity and extent of atrophy, intestinal metaplasia, and presence of dysplasia at original detection
  - Pre-neoplastic lesions regress at a rate equal to the square of time in patients rendered free of H. pylori infection
  - Patients should be determined to be free of infection via a reliable method at regular time points - for example, HPE should be performed at 3, 6, and 9 months following completion of therapy to confirm eradication (For more information, please see presentation on HPE)

Roesler (2011)
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- H. pylori Clarithromycin resistance: Susceptible or resistant
  - This line gives information on the ability clarithromycin to effectively target the detected HP, if present. Remember that the value is not organism specific; rather, it is patient specific.
  - Furthermore, a resistant value indicates that this antibiotic will likely NOT work in THIS patient, and an alternative should be used to avoid the development of additional resistance.
HPE* (or equivalent test) should be performed at 3, 6, and 9 months following completion of therapy to confirm eradication.

*HP Eradication assay (DRG’s HP stool antigen assay)
Next steps

- Please review additional DRG presentations to help elucidate the choice among antibiotics and appropriate methods to determine eradication.


