20th ECCMID Vienna, Austria 10–13 April 2010

Educational Workshop

EW14: Can we control the development of multiresistant *Helicobacter pylori*?

arranged with the European Helicobacter Study Group (EHSG)

Convenors: **Francis Mégraud (Bordeaux, FR)**
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ESCMID EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES

European Multicentre study on antibiotic susceptibility of *H. pylori*

April 2008-June 2009

Steering committee:
L. Andersen, Y. Glupczynski, A. Hirschl, M. Kist, M. Lopez Brea, F. Mégraud (coordinator)

under the umbrella of the European Helicobacter Study Group

Sponsors: Axcan Pharma, AB bioMerieux

Design of the study

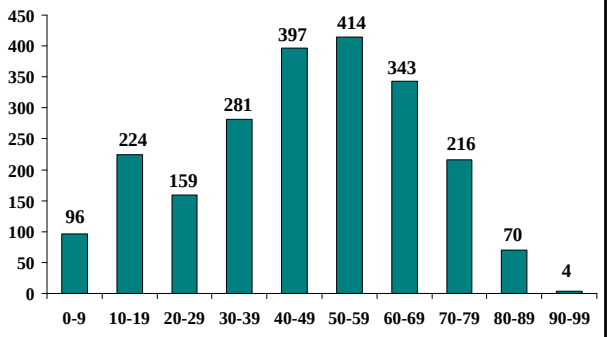
- **1 center per approximately 10 million inhabitants in European countries**
- **Collection of 50 to 100 strains per center**
- **Exclusion of patients who received previous anti-*H. pylori* therapy**
- **Antimicrobial susceptibility using a standardized procedure (Etest) for: clarithromycin, levofloxacin, amoxicillin, tetracycline, rifabutin, metronidazole**
- **On-line reporting**
- **Test of resistance mechanisms (to be performed)**

Distribution per Country (total : 2,204)

Country	No. of Results	%
France	366	16.6
Spain	315	14.2
Italy	202	9.1
Germany	198	8.9
Poland	158	7.1
UK	136	6.1
Croatia	104	4.7
Portugal	102	4.6
Belgium	100	4.5
Greece	100	4.5
Austria	74	3.3
Ireland	74	3.3
The Netherlands	53	2.4
Lithuania	51	2.3
Finland	50	2.26
Norway	46	2.0
Slovenia	45	2.0
Hungary	30	1.36

Mégraud - European multicentre study on *H. pylori* susceptibility

Distribution according to age
(total : 2,204)



Distribution per gender (total 2,204)

Gender	No.	%
Female	1,128	51.18
Male	1,076	48.82

Distribution per country of birth (total 1,781)

	No.	%
Europe	1,578	89.0
Non-European	203	11.0

Distribution according to reason for consultation (total : 1,632)

Reason for consultation	No.	%
Anemia	85	5.2
Dyspepsia	420	25.7
Epigastric pain	740	45.3
Hemorrhage	52	3.1
Other	335	20.5

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Distribution according to endoscopy results (total : 1,630)

Endoscopy results	No.	%
Erosions	136	8.3
Gastric malignancy	10	0.6
Inflammation	853	52.3
Normal	254	15.5
Ulcer	326	20.0
Ulcer scar	51	3.1

H. pylori antibiotic resistance in Europe (2008-2009) (total : 2,204)

ATB	No. of Resistant	% Resistant
Clarithromycin	421	19.10
Amoxicillin	23	1.04
Levofloxacin	273	12.38
Tetracycline	14	0.63
Rifabutin	26	1.18
Metronidazole	729	33.07

H. pylori antibiotic resistance in Europe (2008-2009) (Adults : 1,893)

ATB	No. of Resistant	% Resistant
Clarithromycin	324	17.11
Amoxicillin	22	1.16
Levofloxacin	266	14.05
Tetracycline	14	0.74
Rifabutin	26	1.37
Metronidazole	650	34.33

Helicobacter pylori:
Rational Diagnostic Evaluation and Susceptibility Testing

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Guidelines for the management

- Maastricht III Consensus Report (Gut, 2007)
- American College of Gastroenterology Guideline (Am. J. Gastroenterol. 2007)
- Guidelines for the Management of H. pylori Infection in Japan (J. Gastroenterol. 2007, Jap. J. Clin. Med. 2009)
- Third Chinese National Consensus Guidelines (J. Dig. Dis. 2008)
- Asia-Pacific Consensus Guidelines on Gastric Cancer Prevention (J. Gastroenterol. Hepatol. 2008)
- Second Asia-Pacific Consensus Guidelines (J. Gastroenterol. Hepatol. 2009)
- **S3-Guideline H. pylori and Gastroduodenal Ulcer Disease (Z. Gastroenterol. 2009, in German)**

Indications for treatment

- Peptic ulcer
- Functional dyspepsia
- Uninvestigated dyspepsia
- Asymptomatic gastritis
  - Future use of NSAID or ASA medication
- B cell lymphoma-MALT type
- Prevention of gastric cancer in high risk patients
  - Following partial gastric resection
  - Following endoscopic mucosal resection of high-grade dysplasia or early gastric carcinoma
  - In the presence of a positive family history
  - In the presence of high risk gastritis (corpus-dominant, atrophic, intestinal metaplasia)
  - Upon request of the patient
- Other indications
  - Ménétrier's disease
  - Lymphocytic gastritis
  - Idiopathic thrombocytopenic purpura
  - Iron deficiency anemia

Methods for the detection

- Invasive tests
  - Culture
  - Histology
  - Rapid urease test
  - Molecular tests
- Non (minimally)-invasive tests
  - Urea breath tests
  - Stool antigen tests
  - Serology
  - Molecular tests (stool, saliva)

Diagnostics (1)

- Appropriate methods for the diagnosis of HP infection primarily include direct test procedures such as histology, culture, monoclonal antigen stool test and tests utilizing the marked urease activity.
- Selection of the tests to be used will depend on the purpose of the diagnostic evaluation and the particular individual circumstances
  - Clinical indications for endoscopy
  - Prevalence of infection
  - Local availability and reimbursement by social security institutions
  - Confounding factors
    - Low colonization density of the bacterium with preceding PPI or antibiotic therapy, atrophy or MALT lymphoma
    - Irregular distribution
    - Partial gastric resection
    - Gastrointestinal bleeding
    - Overgrowth with urease-forming bacteria

Diagnostics (2)

- For ensuring a reliable HP diagnosis the following minimum time intervals without HP-suppressive therapy should be observed
  - 2 weeks with a PPI therapy
  - 4 weeks with a preceding eradication therapy or any other type of antibiotic therapy
- For a reliable HP diagnosis at least 2 positive test results should be available. This requirement is based on the low and progressively decreasing prevalence (= low predictive value of a positive test result) in most industrialized countries.
- The only notable exception is duodenal ulcer for which a single positive test result (urease test) will already be sufficient for the therapeutic decision.
- Exclusive serologic detection of antibodies against HP or its virulence factors will not be sufficient for a treatment decision.

Diagnostics (3)

- Pathogenicity factors of HP will partly be the determinants for the development of sequelae of gastritis (ulcer and carcinoma); however, routine testing is not recommended.
- Follow-up and verification of therapeutic success by endoscopy is strictly indicated with ulcer disease and MALT lymphoma.
- If follow-up endoscopy is not required, eradication should be verified using C^{13} urea breath test or monoclonal stool antigen test.
- Routine screening for HP reinfection will not be necessary following successful primary eradication.

Susceptibility testing (1)

- Bacterial culture is the prerequisite for comprehensive resistance testing.
- For routine diagnostic evaluation, the E-test is a highly practicable and reliable method for susceptibility testing.
- Non-culture methods will also be available for clarithromycin and for fluoroquinolones.
- Pre-therapeutic resistance situation will also have essential impact on therapeutic results depending on the treatment regimen selected.

Susceptibility testing (2)

- Resistance testing is not necessarily required for initial treatment in a population with low resistance rates or with the use of treatment regimens for which resistances are of minor importance.
- However, resistance data of hitherto untreated patients are of critical importance for appropriate information on the resistance situation!
- Prior to treatment of an HP infection in children and juveniles antibiotic susceptibility testing should be performed.
- As many of the alternative treatment options have not been approved for children or are contraindicated in the pediatric population, it is even more critical than for adults that a maximum eradication rate is to be achieved with the initial therapy.
- Resistance testing after initial treatment failure and initiation of a second-line therapy supported by susceptibility testing is at least recommended in all those cases for which a repeat endoscopy is performed.

Susceptibility testing (3)

- Under adequate consideration of first-line therapy second-line therapy in adults may be initiated without prior resistance testing.
- Selection of the eradication regimen for second-line therapy must adequately consider the antibiotics used in first-line treatment including the likelihood of resistance induction and adequate consideration of individual intolerances.
- If no endoscopy was performed following an initial treatment failure, endoscopy including collection of a biopsy for culture and susceptibility testing should be done upon a repeated treatment failure.
- Resistance to clarithromycin and metronidazole must be expected with a likelihood of about 80% following more than a single treatment failure.
- The primary factors with possible impact on efficacy of HP therapy include treatment compliance, smoking and the extent of acid inhibition.

Multiresistant *Helicobacter pylori*. Has the test and treat concept run out of time?

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The test and treat concept.

- **Test the patient with UBT and treat the patient with amocicillin, clarithromycin and PPI.**
- **This concept has been used in Denmark for more than 10 years.**

Maastricht recommendations vs. Danish practice.

- **Maastricht guidelines recommend endoscopy after the first treatment failure.**
- **Danish practice has included several treatments with the same drugs or clarithromycin exchanged to metronidazole before endoscopy.**

Outcome of the Danish practice

- **250 patients were included.**
- **50 (20%) were culture positive for *H. pylori*.**
- **30% were positive by PCR.**
- **It is our experience that *H. pylori* is more difficult to culture from patients treated several times as compared to untreated patients.**

Susceptibility testing

- **50 *H. pylori* strains were tested for susceptibility to amoxicillin (AC), tetracycline (TC), erythromycin (EM), clarithromycin (CH), ciprofloxacin (CI), levofloxacin (LE), metronidazole (MZ), rifampicine (RB), clindamycine (CM) and meropenem (MP) by E-test or neosesitabs.**

Results

- **All 50 *H. pylori* strains susceptible to amoxicillin (AC), tetracycline (TC), ciprofloxacin (CI), levofloxacin (LE), rifampicine (RB), and meropenem (MP).**

Andersen – Multiresistant *H. pylori*: has the test and treat concept run out of time?

Results

	Metroni-dazole	Clinda-mycin	Erythro-mycin	Clarithro-mycin
Sensitive	**30%**	**49%**	**47%**	**47%**
Resistant	**70%**	**51%**	**53%**	**53%**

Discussion

- **More than 50% of *H. pylori* strains are resistant to at least two of the commonly used drugs for *H. pylori* eradication.**

Discussion

- **Ciprofloxacin, Levofloxacin and tetracycline are not commenly used for *H. pylori* eradication in Denmark.**
- **However, fluconazole resistance is increasing in *Enterobacteriacae*.**

Conclusion

- **The test and treat concept leads to an enormous increase in resistant or multiresistant *H. pylori* when patients are endoscopied.**
- **Therefore, it is recommended to follow the Maastricht recommendations.**