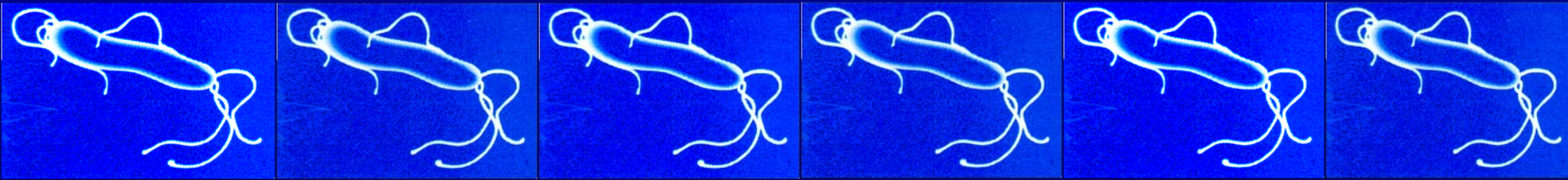


***H. pylori* Therapy**  
**Which Options After a First  
Treatment Failure?**  
(Belgium 2009)

A. Burette

CHIREC/sites de la Basilique & E Cavell, Brussels



# Antibiotics Used for *H. pylori* Eradication

	Drug	Dose
• Standard antibiotics	Amoxicillin	1 g bid
	Metronidazole	500 mg bid/tid
	Clarithromycin	500 mg bid
	Tetracyclin	500 mg qid
• Salvage antibiotics	Levofloxacin	500 mg od/bid
	Rifabutin	150 mg bid
	Furazolidone	100-200 mg bid
• (PPI / Bi)		

# Primary or secondary antimicrobial resistances in clinical strains of *H. pylori*

- **Nitro-imidazoles**
- **Macrolides**
- **Fluoroquinolones**
- **Beta-lactams (Amoxicillin)**
- **Tetracyclines**
- **Nitrofuranes**
- **Rifamycins**

# Hp therapy: “The Treatment Package”

Maastricht 3-2005 Consensus report

- **First line therapy ( $\geq 7$  days)**

(1) PPI + Clarithromycin + Metronidazole <sup>\*(R)</sup>  
(bid) (500 mg bid) (500 mg bid)

CLA-R < 15-20% and MTZ-R < 40%

or

(2) “ “ + Amoxicillin  
(1 g bid)

CLA-R < 15-20% and MTZ-R > 40%

- Malfertheiner P et al. (EHPSG/2005), Gut, 2007, 56: 772-81.
- Chey WD et al. (ACG), AJGE, 2007, 102:1808-25 ( $\geq 10$ -14 days).
- WGO-OMED practice guidelines highlights. WGN, 2007, 11: 22-29.
- Fujioka T et al. (JSHR/2003), JGE, 2007, 42: 3-6.

# Comment traiter l'infection à *Hp* ?

## RECOMMANDATIONS POUR LA PRESCRIPTION

- Prendre le temps d'expliquer le traitement au patient
- Avertir qu'il n'est pas toujours facile à suivre
- Suggérer de préparer à l'avance les prises quotidiennes
- Informer des effets secondaires éventuels
- Avertir de ne pas interrompre le traitement sans avis médical

# **Hp therapy: “The Treatment Package”**

Maastricht 3-2005 Consensus report

- **Second line therapy ( $\geq 7$  days)**

PPI + Bismuth/RBC + Tetracycline + Metronidazole  
(bid) (120 mg qid) (500 mg qid) (500 mg tid)

or

PPI + Amoxicillin or Tetracyclin + Metronidazole  
(bid) (1 g bid) (500 mg qid) (500 mg tid)

- **Third line therapy**

Rescue treatment based on antimicrobial susceptibility testing/Management on a case-by-case basis

# *Hp* Eradication Failures

- **AB-resistance**
- **Lack of compliance**  
(QID, poor tolerability, longer duration,...)
- Metabolism of PPI (CYP2C19) (MDR1)  
(EM<<PM)
- Impaired host mucosal immunity  
(↓IL-4 secretion)
- Cag A negative
- Internalisation of *Hp*
- Coccoid forms??

# *Hp* Antibiotic Resistance: Why it is important

## *Hp* antimicrobial resistance

⇒ ↓ eradication rates

- **MTZ** Resistance adversely affects the success rate of MTZ-containing PPI-based triple therapies by  $\approx$  25-30%
- **CLA** Resistance adversely affects the success rate of CLA-containing PPI-based triple therapies by  $\approx$  50-60%

# *Hp* Antibiotic Resistance: Why it is important

## Emergence of Resistance

after triple therapies failures:

- After exposure to **CLA**
  - ⇒ *CLA-resistant* strain in  $\approx 25\%$  (0-50%)
- After exposure to **MTZ**
  - ⇒ *MTZ-resistant* strain in
    - $\approx 50\%$  when the infecting strain is *CLA-sensitive*
    - $\geq 50-100\%$  when the infecting strain is *CLA-resistant*

# *Hp* Antibiotics Resistance Prevalence

- **Primary resistance in Belgium (2008)**
    - for Imidazoles  $\pm$  30 % (20-45%) (=)
    - for Macrolides  $\pm$  15 % (10-20%) (=)
    - for Fluoroquinolones  $\pm$  25 % (20-30%) ( $\nearrow$ )
- ...and 5-16% strains are multi-resistant

(Amoxy: <1%; Tetracyclines:  $\leq$ 2%)

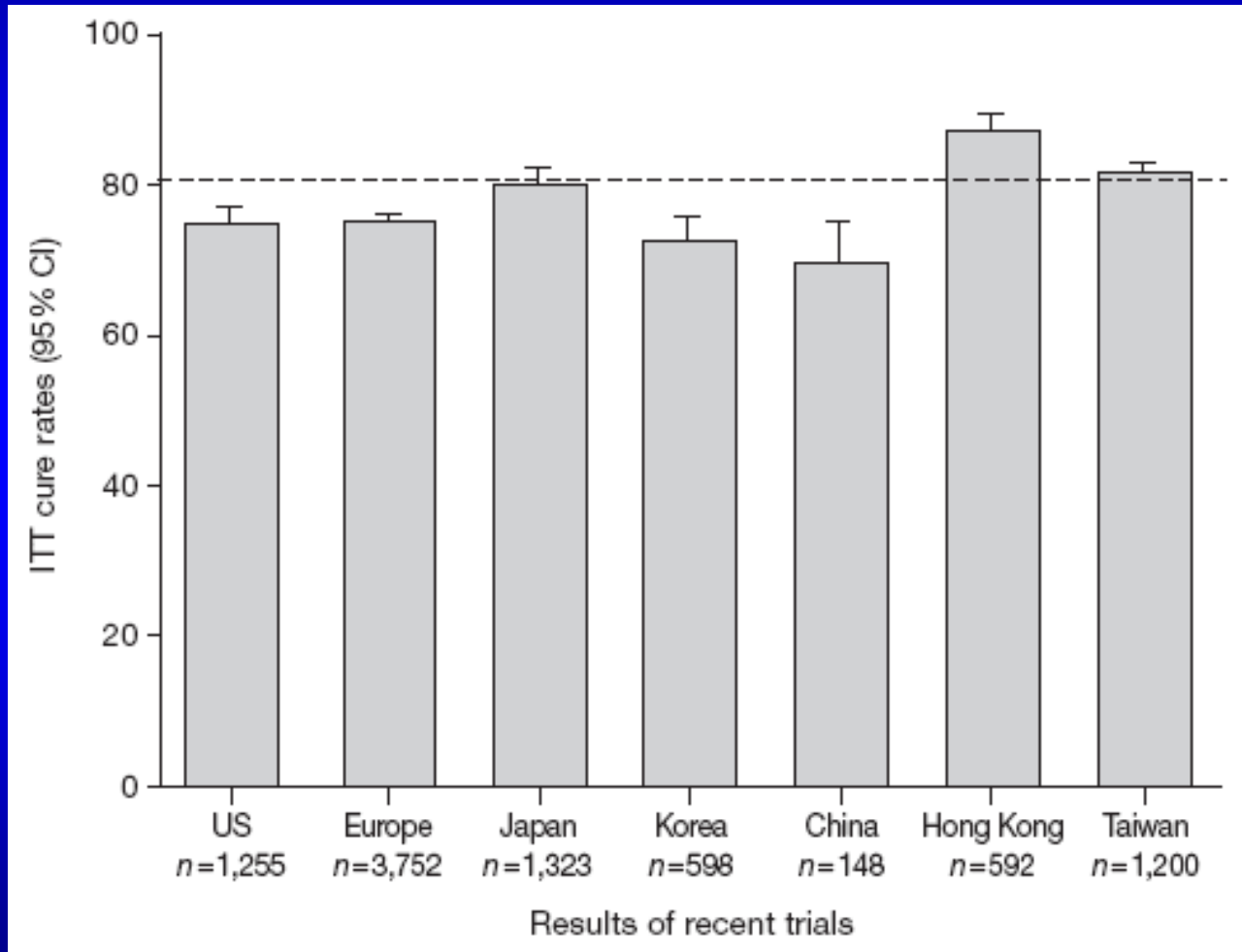
# Prevalence of *Hp* Double and Triple Primary Resistance to Imidazoles, Macrolides and/or Quinolones (%) in Belgium in 2008

Centres	Double R	Triple R
Brussels <sup>1</sup> (consecutive pts)	13.4 (n=97)	1.1 (n=97)
Brussels <sup>2</sup>	16.1* (n=294)	4.3 * (n=294)
Brussels <sup>4</sup>	11.4 (n=70)	4.3 (n=70)
Mont-Godinne <sup>2</sup>	16.1* (n= 74)	4.3 * (n=74)

<sup>1</sup>Burette et al (CHIREC/Basilique), <sup>2</sup>Glupczynski et al (St-Luc), <sup>2</sup>Glupczynski et al (Mt-Godinne),  
<sup>4</sup>Mana et al (UZB)

# Performance of Triple Therapies

## Actual Cure Rates are 70-79% (ITT)



Results of recent comparison studies with >100 pts (PPI+A+C)

# Eradication Rates in Large US trials of PPI Triple Therapy

Author/ reference/ year	Regimen										Duration of therapy (days)	Intent to treat Eradication Rate	95% CI
	A	C	T	B	M	E	O	L	P	R			
Laine 15/1998	●	●					●				10	75%*	(70 - 81)
Fennerty 16/1998	●	●						●			10	81%	(74 - 88)
	●	●						●			14	82%	(74 - 88)
Laine 13/2000	●	●				●					10	78%*	(70 - 85)
Laine 14/2003			●	●	●		●				10	88%	(82 - 93)
	●	●					●				10	83%	(77 - 90)
Bochenek 17/2003	●	●							●		7	65%*	(57 - 73)
		●			●				●		7	77%*	(69 - 84)
Vakil 18/2004	●	●								●	7	77%	(71 - 83)
	●	●								●	10	78%	(72 - 84)
	●	●					●				10	73%	(67 - 79)

- **Currently recommended PPI-based triple therapies are losing their efficacy**  
**Failures rates commonly exceed 20%**
- **Regimens efficacious in the presence of (CLA) drug resistance are needed**

# How to improve 1st Line anti-*Hp* Therapies?

- **Extend the duration of therapy**  
7 > 10 > 14 days:  
controversial results (Europe =; USA +)
- **Avoid systematically CLA when local prevalence of primary R  $\geq$  20%**
- **Routine Antimicrobial sensitivity testing before therapy?**

# General Considerations for Rescue anti-*Hp* Therapies

- Never use CLA, (MTZ) or LVX if already included in the 1st line therapy
- AMX: soluble > tablets
- MNZ: 500 mg tid > bid
- Consider prolongation of therapy 7 > 10 > 14 d
- Antimicrobial susceptibility testing if possible
- Consider regimen combining PPI + AMX + AB not included in previous regimens (levofloxacin, rifabutine, furazolidone)
- Post treatment testing mandatory to confirm cure!

# Rescue anti-*Hp* Therapies?

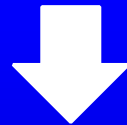
	ITT score
• Bi-based Quadruple therapies	
• <b>Quinolone-based therapies (Levofloxacin)</b>	≥ 80%
• Rifabutine-based therapies	
• Furazolidone-based therapies	
• <b>Sequential therapy (10d)</b>	≥ 90%
• <b>Concomitant therapy (7d)</b>	≥ 90%

# Quinolone-based Triple Therapy

7 to 10 days

PPI 20 mg bid

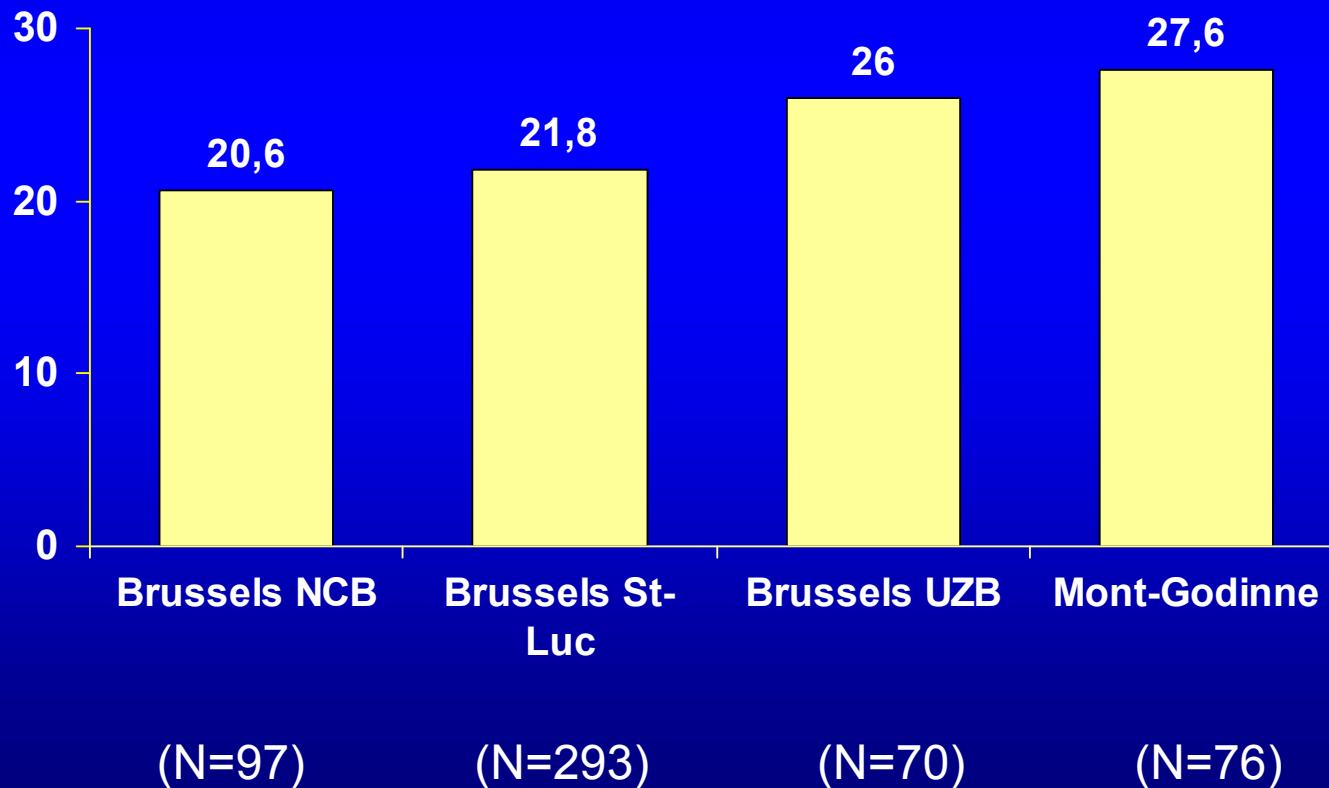
LVX 250-500 mg bid



⇒ Eradication  $\geq$  80%

# Prevalence of *Hp* Primary Resistance to Fluoro-quinolones (%) in Belgium (2008)

% resistance to ciprofloxacin



# Prevalence of *Hp* Primary Resistance to Quinolones (%) in Belgium

Centres	2004	2006	2008
Brussels <sup>1</sup> (consecutive pts)	14.8 (n=115)	16.7 (n=89)	20.6 (n=97)
Brussels <sup>2</sup>	15.0 (n=107)	14.0 (n=150)	21.8 (n=293)
Brussels <sup>4</sup>			26.0 (n=70)
Mont-Godinne <sup>3</sup>	18.4 (n=38)	17.0 (n=88)	27.6 (n=76)

<sup>1</sup>Burette et al (CHIREC/Basilique), <sup>2</sup>Glupczynski et al (St-Luc), <sup>3</sup>Glupczynski et al (Mt-Godinne), <sup>4</sup>Mana et al (UZB)

# Sequential Therapy

	D1 – D5	D6 – D10
PPI x2		
Amoxicillin 1g x2		
Clarithromycin 500 mg x2		
Metronidazole 500 mg x2		

Eradication = 51/52 (98%) patients

# Sequential Therapy

## Theoretical Basis

- Efficacy of therapy inversely linked to bacterial mucosal density
- Amoxicillin alteration of bacterial membrane  
⇒ prevention of CLA resistance
- > Usefulness of pretreatment with amoxicillin before clarithromycin therapy

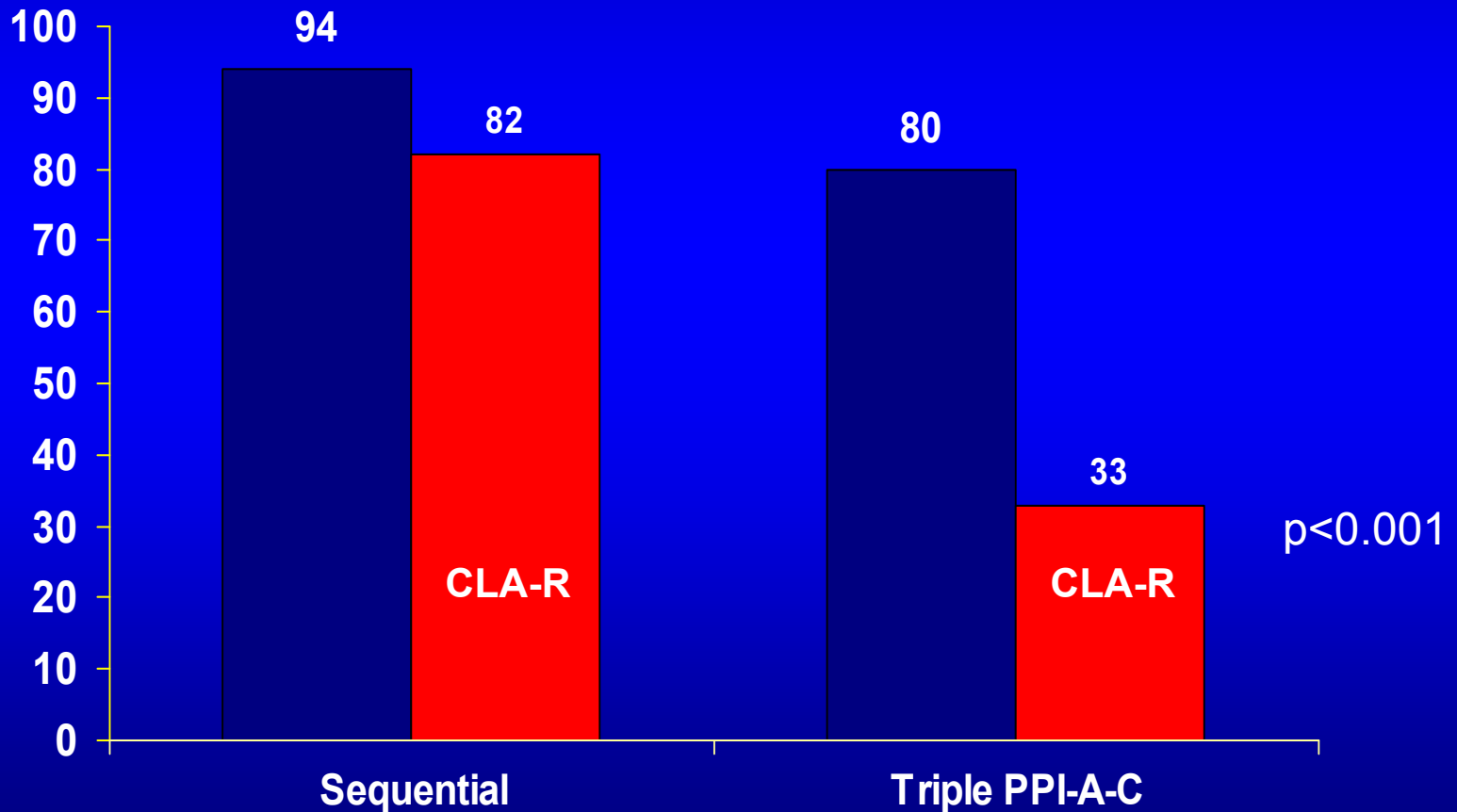
# Overall Eradication Rates after Sequential Therapy in Italy

Author	Year	Centres involved	Patients enrolled	Patients cured	ITT (%)
Zullo et al	2000	1	52	51	98
De Francesco et al	2001	2	63	61	93.8
Focareta et al	2002	1	94	90	95.7
Zullo et al	2003	8	522	481	92
Hassan et al	2003	1	152	142	93.4
Forareta et al	2003	1	174	166	95.4
De Francesco et al	2004	1	162	151	93.2
De Francesco et al	2004	2	45	43	95.5
De Francesco et al	2004	2	116	110	94.8
Francavilla et al	2005	1	38	36	94.7
Zullo et al	2005	3	89	84	94.4
Zullo et al	2005	1	40	38	95
Saccianoce et al	2005	2	72	68	94.4
Francavilla et al	2006	1	40	33	82.5
Vaira et al	2007	2	146	133	91.1
Total			1805	1687	93.5

# Comparison Sequential Therapy vs PPI-AMX-CLA (7-10d)

Pooled data analysis (15 studies/1805 pts)

% cure rate



# Overall Eradication Rates after Sequential Therapy outside Italy

Author	Country	Year	Centres involved	Patients enrolled	Patients cured	ITT (%)
Choi WH et al	Korea	2008	1	77	60	77.9
Sanchez-Delgado et al	Spain	2008	6	139	117	84.2
Uygun A et al <sup>(14 d)</sup>	Turkey	2008	1	150	109	72.6
Shehada S et al	Israel	2007	1	5	1	20.0
Park S et al <sup>DDW09</sup>	Korea	2009	1	26	21	80.8
Nathevut S et al <sup>DDW09</sup>	Thailand	2009	1	78	75	96.1
Kalach N et al <sup>(ped)</sup>	France	2007	1	13	11	84.6
Total				488	394	80.7

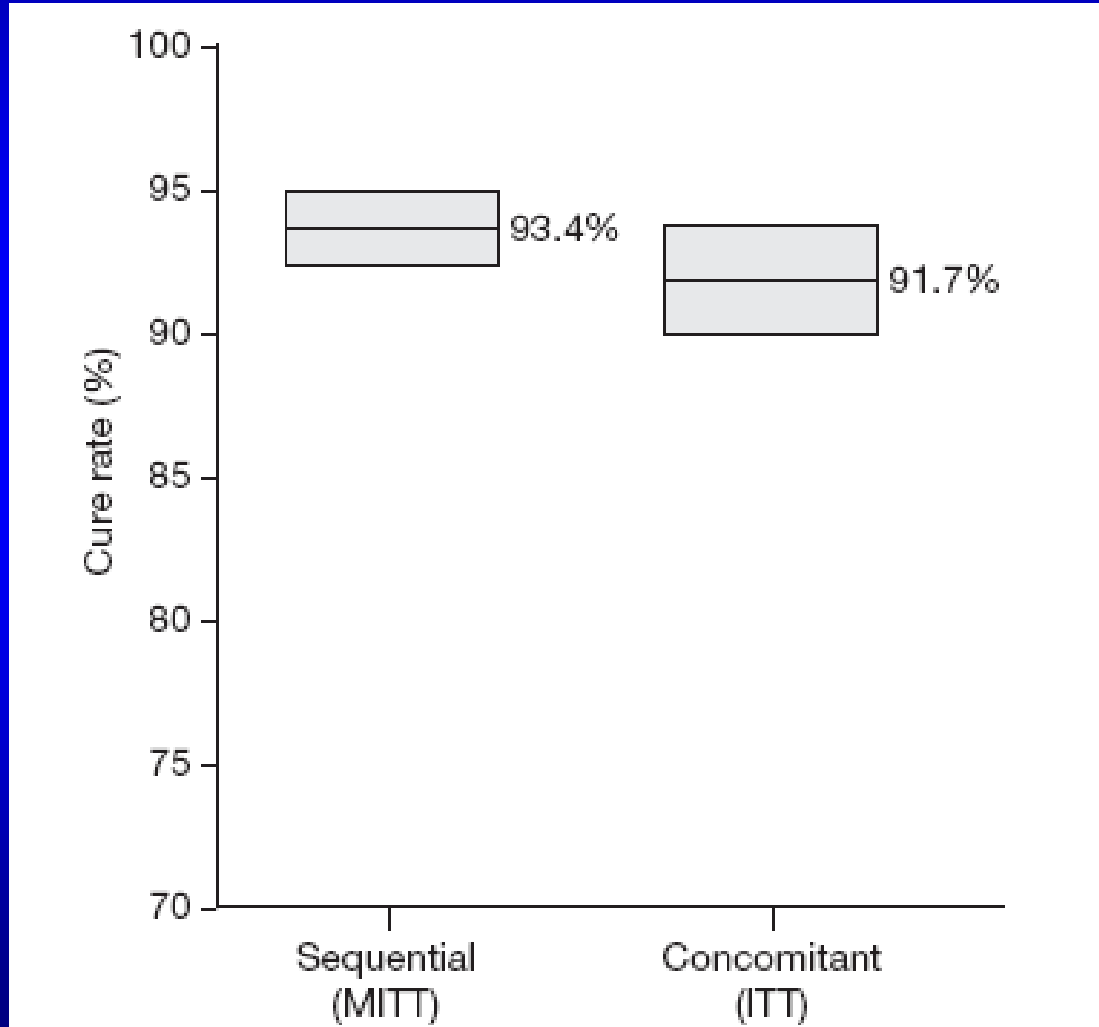
# Concomitant Therapy

	D1 – D7
PPI x2	
Amoxicillin 1g x2	
Clarithromycin 500 mg x2	
Metronidazole 500 mg x2	

Eradication (mean) = 92%

# Sequential Therapy vs Concomitant Therapy

(10d) (7d)



Sequential Tx (10 d):  
16 studies  
1.805 pts

Concomitant Tx (3-7 d):  
9 studies  
715 pts

# High dose Dual Therapy

PPI 80 mg bid  
or 40 mg qid

+

AMX 1 g tid  
or 750 mg qid

**14 days**



⇒ Eradication ITT  $\geq 75\%$

Kita T et al., Biol Pharm Bull, 2002

Furuta T et al., Pharmacogenetics, 2001

Furuta T et al., Hepatogastroenterology, 2003


Miehlhe S et al., Helicobacter, 2003, 8: 310-19

# Stratégie Thérapeutique: depuis 15 ans

## Traitements Probabilistes: Test & Treat

---

- Taux de guérison obtenus chutent progressivement
  - AB > Pression de sélection > Résistance > Echec thérapeutique
- Nécessité impérative d'un contrôle d'éradication post traitement!

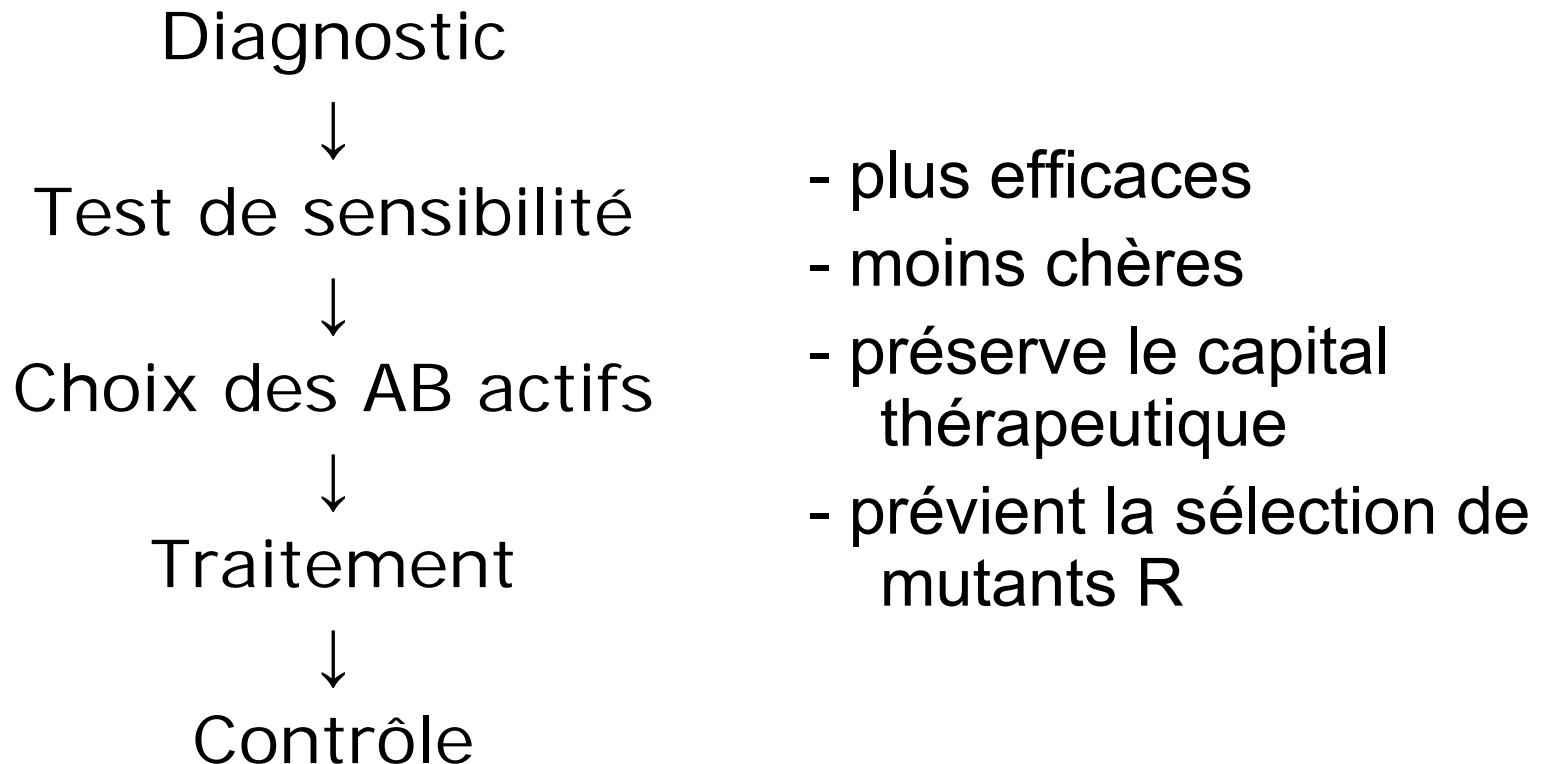
- 
- La nette augmentation de prévalence des résistances « primaires »

---

explique la chute des taux de réussite des traitements probabilistes
  - Peut-on continuer à avoir une stratégie thérapeutique probabiliste qui est de moins en moins efficace et qui facilite l'émergence et la diffusion de résistances?
  - Alternative?

# Stratégie Thérapeutique basée sur les résultats des tests de sensibilité aux AB

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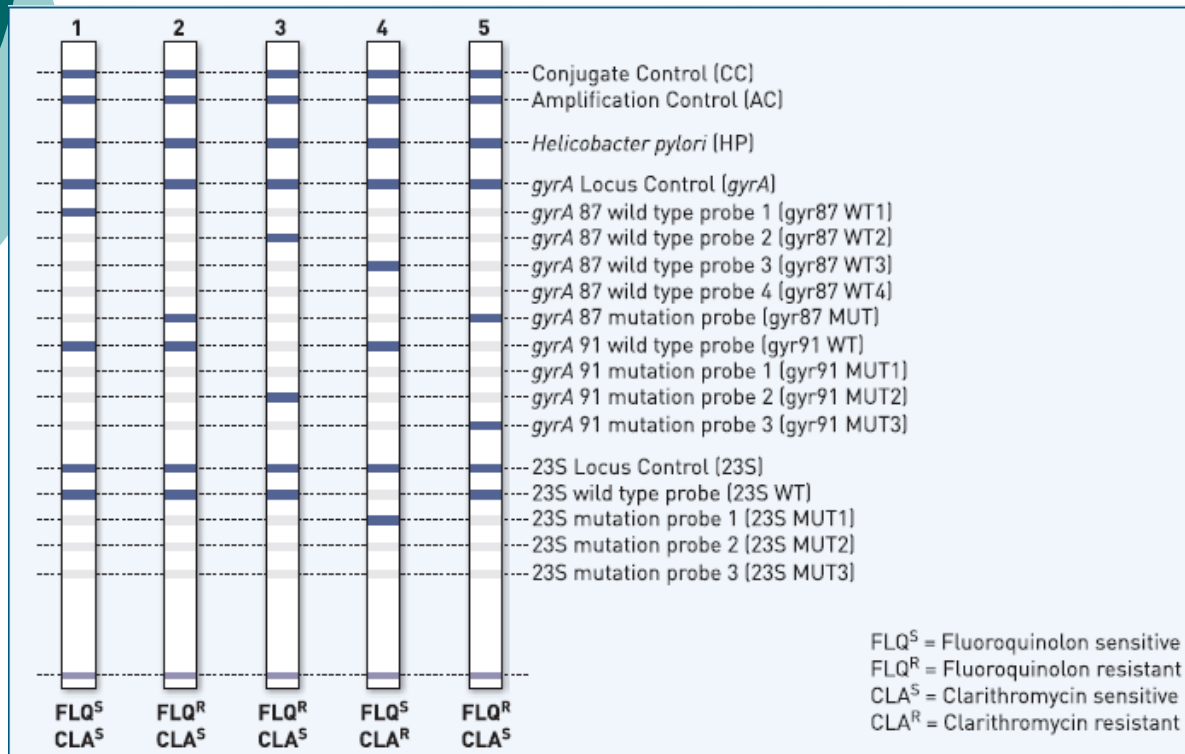
# Stratégie Thérapeutique basée sur les résultats des tests de sensibilité aux AB

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## Antibiogramme systématique:

- Cultures
  - délicate, longue (12j), pas dans de Nb centres
  - conditions d'acheminement au laboratoire!
- Tests moléculaires de dépistage des mutations associées à la résistance aux AB
  - rapides (3-24h), faciles à réaliser
  - conditions de transport bcp plus simples!

# Tests PCR: Alternative à l'Antibiogramme



**Helico DR:  
premier test  
moléculaire  
commercialisé**

- **GenoType® HelicoDR** enables to identify
- fluoroquinolone resistance by detection of the most common mutations in the *gyrA* gene
- clarithromycin resistance by detection of the most common mutations in the 23S rRNA gene of *H. pylori* including differentiation of the four wild types.

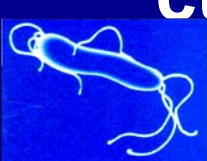
# Conclusions

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- Nécessité de réactualiser les consensus actuels
- Stratégie thérapeutique basée sur les tests de sensibilité:
  - plus efficaces
  - moins chères
  - préserve le capital thérapeutique
  - évite la sélection de mutants R
- Rendre cette stratégie accessible à tous les malades infectés:
  - ABiogramme à réapprendre
  - tests PCR à développer, à commercialiser, à diffuser (cf. GEFH, 2009)

# Conclusions

- **Reconsider indication of therapy: cost/risks vs potential benefit**
- **Importance of prescription counseling and recommendations!**
- **Treatment failures select less compliant pts infected with higher risk of (multi-) resistant strains**
- **Post treatment testing mandatory to confirm cure!**



# Conclusions

## Rescue Therapeutic Options

- **Sequential (5+5d) or Concomitant Tx (7d)** (PPI? AMX? MNZ tid?...)
- **Levofloxacin-based triple therapy**
- **High dose dual PPI-AMX therapy**
- **Future: Suceptibility testing based therapies**  
(2<sup>nd</sup> line? 1<sup>st</sup> line?)  
Access to Bi again?  
New drugs?...  
Vaccine?...





# Conclusions

- High rates of primary resistance of *Hp* strains to Nitroimidazoles, Quinolones and Macrolides are observed in four different Belgian centres
- Average level of primary resistance to MTZ (25-45%) remains comparable to those observed these last years
- CLA-resistance seems to decrease slightly (12-20%) but LVX-resistance is increasing with R-rates > 20% in all the centres
- Also worrying is the progressive increasing rates of double or even triple-resistant strains over the last years
- Large variations in resistance rates by centres do occur, especially to CLA



# Conclusions

- Confirmation of a uniformly high and increasing rate of resistance to ciprofloxacin (21-28%) with cross-resistance to other fluoroquinolones is found among *Hp* strains
- Low level of resistance to amoxicillin (<0.1%) and tetracycline ( $\approx 1\%$ )
- Multiple drug resistance ( $\geq 2$  agents) in about 15% of all strains (clari + metro resistance in 7-15% of all isolates)



# Indications for *H.pylori* Eradication (2009)

- Strongly recommended
  - Peptic Ulcer Disease
  - Gastric MALT
  - Atrophic Gastritis
  - Partial Gastrectomy for Gastric Cancer
  - 1st degree relatives of Gastric Cancer patient
- Other indications
  - Non Ulcer Dyspepsia
  - Long term PPI use
  - Long term NSAID use
  - Unexplained Iron Deficiency Anaemia
  - Thrombotic Thrombocytopenic Purpura
  - Patient's own wish