Clinical relevance of resistant strains of *Helicobacter pylori*: a review of current data

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Summary
Acquired resistance of *Helicobacter pylori* to metronidazole and clarithromycin has been reported, with metronidazole resistance being very common. This has an important clinical impact on dual therapies, as well as on the standard triple therapies. However, when antisecretory drug based triple therapies with amoxycillin or clarithromycin and metronidazole are used, the resistance can be overcome in up to 75% of the cases in most of the studies. Clarithromycin seems to be a better choice than amoxycillin to achieve this goal. Nevertheless, resistance to metronidazole remains a risk factor for treatment failure.

The most precise information comes from studies in which minimum inhibitory concentrations (MICs) are reported as well as whether the strain is susceptible or resistant.

Few data are available from clinical trials to measure the impact of clarithromycin resistance. However, such resistance seems to have a negative impact on the clinical outcome of treatment.

It is of great importance that *H pylori* resistance is closely monitored in the future.

Introduction

Acquired resistance is a concern with respect to two of the major antibiotics used in regimens to eradicate *H pylori*, metronidazole and clarithromycin.[1] Resistance is defined by a cut off value, which depends on the minimum inhibitory concentration (MIC) of the strains and on the concentration of antibiotic that can be achieved in the tissue by a given therapeutic dose. Resistance to antibiotics is considered to be a major cause of failure in the treatment of bacterial infections in general and *H pylori* infection in particular. However, the clinical relevance of this concept has been challenged because resistance to clarithromycin is rare and resistance to metronidazole seems to be variable. We will review the data published in clinical trials in which the susceptibility of primary isolates has been determined.

Consequences of resistance to metronidazole

LIMITS OF THE METHODS USED TO DETERMINE METRONIDAZOLE RESISTANCE

Numerous methods have been used to determine metronidazole susceptibility or resistance of *H pylori*,[1] and there is no standardisation. The correlation between these different methods is usually poor and raises the question of which are "true" results. Since the agar dilution method is the reference method for other bacteria, we think that it should also be used as the reference method for *H pylori*.

Another important point is the relative lack of reproducibility for a given method. Cederbrant *et al* introduced the concept that the redox potential may influence the result.[2] Indeed this parameter is usually not controlled and therefore may account for this lack of reproducibility.

These problems may explain the variability found in metronidazole resistance in *H pylori*, for which the molecular mechanism is not yet known.

There is cross resistance between metronidazole and tinidazole, the other metronidazole sometimes used.

METRONIDAZOLE RESISTANCE IN DUAL THERAPIES

Metronidazole has been used with bismuth salts, amoxycillin, and clarithromycin for treatment periods of one or two weeks. In dual therapies that combine bismuth salts and metronidazole, eradication rates range from 75 to 91% for susceptible strains and from only 16 to 22% for resistant strains[3–5] except in one study (87 *v* 72% respectively).[6]

When a combination of amoxycillin and tinidazole was given for seven days in the study by Glupczynski *et al*,[7] none of the 13 metronidazole resistant strains was eradicated. Using the same dual therapy but with metronidazole instead of tinidazole and a treatment period of 10 days instead of seven, the same authors succeeded in eradicating 21 of 22 metronidazole susceptible strains but only two of eight metronidazole resistant strains.[8]

With clarithromycin, Bazzoli *et al* found a rate of eradication of 60% in metronidazole susceptible strains and 30% in resistant strains.[9]

In the MACH2 study,[10] better results were obtained but there was still a significant difference between metronidazole susceptible (86%) and metronidazole resistant (43%) strains.

METRONIDAZOLE RESISTANCE IN "STANDARD" TRIPLE THERAPIES

Regardless of the antibiotic given with metronidazole, either amoxycillin or tetracycline, and regardless of the duration of treatment, significant differences in eradication rates were found between susceptible and resistant strains (table 1).

When the duration of treatment was decreased to four days, Glupczynski *et al* still obtained a cure rate of 47–60% for susceptible strains while none of the resistant strains was eradicated.[8]

Only the results of Lynch *et al*,[17] who gave the regimen five times daily, and those of Lerang *et al*[18] are discrepant with the previous ones. The latter results are surprising especially taking into account that (*a*) they used a cut off value of

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Table 1 Impact of metronidazole resistance on the eradication of Helicobacter pylori with the standard triple therapy: bismuth salts-amoxycillin or tetracycline-metronidazole or tinidazole (Bi, A, M or Ti) or (Bi, Te, M or Ti)

Reference	Type of study	Type of treatment and duration	No of patients	Eradication (%)		
				Overall	Susceptible	Resistant
Logan *et al* [11]	Non-randomised, open, monocentre	Bi A M 1 week (M 3 last days)	106	72 (76/106)	93 (40/43)	19 (4/21)
Rautelin *et al* [12]	Non-randomised, open, monocentre	Bi A M 2 weeks	86	81 (70/86)	91	63
Bell *et al* [13]	Non-randomised, open, monocentre	Bi Te M 2 weeks	40	–	91 (19/21)	32 (6/19)
Bell *et al* [14]	Non-randomised, open, monocentre	Bi Te M 2 weeks	43	–	91 (20/22)	33 (7/21)
Burette *et al* [15]	Randomised, double blind, monocentre	? 2 weeks	–	–	97	63
Lian *et al* [16]	Non-randomised, open, monocentre	Bi Te M 2 weeks	–	–	86 (51/59)	42 (6/14)
Lynch *et al* [17]	Non-randomised, open, monocentre	Bi Te M 2 weeks	45	58 (26/45)	56 (9/16)	67 (4/6)
Lerang *et al* [18]	Non-randomised, open, monocentre	Bi Te M 2 weeks	–	–	90 (n=50)	96 (n=23)
Midolo *et al* [19]	Non-randomised, open, monocentre	Bi A M 1 week (Bi 2 weeks)	37	–	68	17
Gisbert *et al* [20]	Non-randomised, open, monocentre	Bi Te M 2 weeks	57	74 (42/57)	87	25
Glupczynski *et al* [8]	Randomised, open, monocentre	Bi A M 10 days (A 16 days)	–	–	96 (23/24)	71 (10/14)
Glupczynski *et al* [8]	Randomised, open, monocentre	Bi A Ti 4 days	–	–	60 (30/50)	0 (0/15)
Glupczynski *et al* [8]	Randomised, open, monocentre	Bi Te Ti 4 days	–	–	47 (17/36)	0 (0/12)

16 mg/l for resistance (instead of 8 mg/l) and (*b*) their proportion of resistant strains was high. They claimed an eradication rate of 90 and 95% for metronidazole susceptible and resistant strains respectively.[18]

METRONIDAZOLE RESISTANCE IN ANTISECRETORY DRUG BASED TRIPLE THERAPIES WITH AMOXYCILLIN

A few authors have reported eradication rates according to the susceptibility or resistance of *H pylori* to metronidazole, and again a difference can be noted (table 2). Bell *et al*[14] performed two studies with a 14 day regimen and omeprazole as the antisecretory agent. The rate of eradication increased from 75% for metronidazole resistant strains to 96–100% for metronidazole susceptible strains.[14 21] Similar results were obtained by Lerang *et al*[22] with a 10 day regimen, and by Thijs *et al*[23] with a seven day regimen (69 *v* 95%). Bouchard *et al*[24] using lansoprazole as the antisecretory agent and a treatment period of 10 days obtained an eradication rate of 90 and 45% for metronidazole resistant and susceptible strains respectively.

Adamek *et al*[25] were unable to cure four patients harbouring metronidazole resistant strains, but surprisingly Bell *et al*,[14] using a triple therapy for seven days, obtained better results on metronidazole resistant strains than when they gave it for 14 days.

When ranitidine was used instead of a proton pump inhibitor (PPI), the eradication rate decreased from 95 to 83% for metronidazole susceptible strains and from 40 to 16% for metronidazole resistant strains.

METRONIDAZOLE RESISTANCE IN ANTISECRETORY DRUG BASED TRIPLE THERAPIES WITH CLARITHROMYCIN

As shown in table 3, in six of eight studies performed there was a significant difference between the cure rate obtained with metronidazole susceptible (88–100%) and resistant strains (48–82%). However, only one study reported a low cure rate (48%) with a metronidazole resistant strain, the others producing a cure rate of 75% or more. Moayyedi *et al*[28] and Lerang *et al*[22] did not obtain different eradication rates for the two groups.

More recently, in a German multicentre study using a pantoprazole based triple therapy in which 188 strains were cultured, the eradication rate fell from 90% when the strains were metronidazole susceptible to 74% when they were resistant.[30]

Yousfi *et al*[31] were the only ones to use ranitidine in association with clarithromycin and metronidazole for 14 days, but no difference was observed between metronidazole resistant and susceptible strains (80 *v* 77%).

METRONIDAZOLE RESISTANCE IN QUADRUPLE THERAPIES

Quadruple therapies—that is, standard triple therapies plus a PPI—have been proposed as the best eradication regimens to cure patients infected by resistant strains (table 4). de Boer *et al*[34] administered this treatment for four days to 54 patients. They cured 91% of their patients, 33% of those harbouring metronidazole resistant strains and 95% of those harbouring susceptible strains. When they increased the treatment period to seven days and used lansoprazole instead of omeprazole in 67 patients, the rates were 89 and 100% respectively.[37] Similar results were reported by Hosking *et al*.[41]

ERADICATION ACCORDING TO MIC VALUES

In the results presented, the strains were categorised as susceptible or resistant by the authors, but reference to the MIC was not always made. In a few studies, it is possible to look at the results according to the MIC.

Table 2 Impact of metronidazole resistance on the eradication of Helicobacter pylori with the triple therapy: omeprazole or lansoprazole-amoxycillin-metronidazole (OAM, LAM)

Reference	Type of study	Type of treatment and duration	No of patients	Eradication (%)		
				Overall	Susceptible	Resistant
Bell *et al* [14]	Non-randomised, open, monocentre	OAM 14 days	263	89 (234/263)	96(53/55)	75 (64/72)
Bell *et al* [21]	Randomised, double blind, monocentre	OAM 14 days	60	92	100(33/33)	75 (9/12)
Bouchard *et al* [24]	Randomised, double blind, multicentre	LAM 10 days	93	–	90	45
Lerang *et al* [22]	Randomised, double blind, monocentre	OAM 10 days	77	91 (70/77)	96(48/50)	77 (17/22)
Thijs *et al* [23]	Non-randomised, open, monocentre	OAT 7 days	97	89	95(80/84)	69 (9/13)

Table 3 Impact of metronidazole resistance on the eradication of Helicobacter pylori with triple therapies comprised of omeprazole or lansoprazole or pantoprazole-clarithromycin-metronidazole or tinidazole (OCM, LCM, PCM, OCT)

Reference	Type of study	Type of treatment and duration	No of patients	Eradication (%)		
				Overall	Susceptible	Resistant
Xia *et al* [26]	Non-randomised, open, monocentre	OCM 1 week	57	79 (45/57)	100 (34/34)	48 (11/23)
Peitz *et al* [27]	Randomised, monocentre	OCM 1 week	94	91 (86/94)	100	82
Moayyedi *et al* [28]	Non-randomised, open, monocentre	OCT 1 week	141	–	90 (62/69)	93 (42/45)
Bazzoli *et al* [9]	Randomised, double blind, monocentre	OCT	32	94 (30/32)	100 (18/18)	75 (3/4)
Harris *et al* [29]	Non-randomised, open, multicentre	LCM 1 week	71	86 (61/76)	92 (22/24)	75 (12/16)
Lerang *et al* [22]	Randomised, double blind, monocentre	OCM 10 days	76	95 (72/76)	94 (45/48)	94 (17/18)
Lind *et al* [10]	Randomised, double blind, multicentre, MIC centralised	OCM 1 week	120	91	95	76
Kist *et al* [30]	Randomised, double blind, multicentre, MIC centralised	PCM	188		90	74

MIC, minimum inhibitory concentration.

Table 4 Impact of metronidazole resistance on the eradication of Helicobacter pylori with the quadruple therapies, according to length of treatment

Reference	Length of treatment (days)	Eradication (%)		
		Overall	Susceptible	Resistant
Tucci *et al* [32]	1	72 (23/32)	72 (23/32)	0/0
Tucci *et al* [33]	2	90 (27/30)	90 (27/30)	0/0
de Boer *et al* [34]	4	91 (49/54)	95 (38/40)	33 (1/3)
de Boer *et al* [35]	7	98 (53/54)	96 (27/28)	100 (3/3)
de Boer *et al* [36]	7	93 (37/40)	93 (26/28)	100 (5/5)
de Boer *et al* [37]	7	91 (61/67)	89 (33/37)	100 (3/3)
Borody *et al* [38]	7	95 (140/147)	97 (93/96)	95 (35/37)
Borody *et al* [39]	12	98 (122/125)	98 (93/95)	97 (29/30)
Seppala *et al* [40]	14			88 (42/48)

In a study by Xia *et al*,[26] who used a standard triple therapy on 121 patients, the eradication rates were 96% (MIC <4 mg/l), 62.5% (MIC 4–8 mg/l), and 53% (MIC >8 mg/l).

In a small number of cases, Moayyedi *et al*[28] obtained an eradication rate of 70% in metronidazole susceptible strains compared with 30% in resistant strains when the cut off value for resistance was 32 mg/l, but they observed no difference when the disk diffusion method was used.

In two large multicentre studies, the MICs were determined by agar dilution in our laboratory and the cure rate expressed according to the MIC.[10 24] Despite the fact that in the study using amoxycillin, the treatment was given for 10 days instead of seven, there was a definite advantage to using the clarithromycin based triple therapy on metronidazole resistant strains.

In summary, the results observed are heterogeneous. However, there is a trend toward a lower success rate in metronidazole resistant strains. This trend becomes more marked in large studies, where MICs have been determined by the most accurate method. Clarithromycin is a better choice than amoxycillin as a second antibiotic.

Consequences of resistance to clarithromycin

DETECTION OF CLARITHROMYCIN RESISTANCE

The mechanism involved in clarithromycin resistance is now well known even at the molecular level.[42] When an *H pylori* strain is resistant to clarithromycin, there is a decrease in binding of the compound to ribosomes, and this is associated with a point mutation found on the 23S ribosomal RNA gene in one of two positions (2143 and 2144).[43] The consequence is a high level of resistance, which is therefore easy to detect phenotypically, whatever the method used. Furthermore, there are now molecular tests that can be applied after amplification of the 23S ribosomal RNA gene. Besides sequencing, polymerase chain reaction-restriction fragment length polymorphism and hybridisation have been used.[44]

Cross resistance occurs between all macrolides, but clarithromycin resistance is rarely found, which limits the data available to evaluate its impact.

CLARITHROMYCIN RESISTANCE IN DUAL THERAPIES

Only one study, the MACH2 study, has been performed to monitor possible *H pylori* resistance to dual therapies in which clarithromycin was combined with another antibiotic—for example, amoxycillin or metronidazole. In this study, only one strain was resistant to clarithromycin in the clarithromycin-amoxycillin group, and it was not eradicated, and three in the clarithromycin-metronidazole group, which were also not eradicated.[10]

In dual therapies in which an antisecretory agent is given with clarithromycin for 14 days, early studies have shown a difference in the eradication rate between susceptible and resistant strains (table 5), but the number of resistant strains was very low.

More recently, in a multicentre study in which the level of clarithromycin resistance was higher, there was a significant difference in the rate of eradication between clarithromycin susceptible strains (74%) and clarithromycin resistant strains (40%). In contrast, this difference did not exist when ranitidine-bismuth citrate was used instead of omeprazole (96 *v* 92%).[47] This result may be linked to the antimicrobial activity of bismuth, which acts

Table 5 Impact of clarithromycin resistance on the eradication of Helicobacter pylori with dual therapies comprised of an antisecretory drug and clarithromycin

Reference	Type of study	Type and duration of treatment	No of patients	Eradication (%)		
				Overall	Susceptible	Resistant
Cayla *et al* [45]	Open, monocentre	OC 2 weeks	35	60 (21/35)	64 (20/31)	25 (1/4)
Schültze *et al* [46]	Randomised, monocentre	RC 2 weeks	39	56 (26/39)	62 (21/34)	20 (1/5)
Mégraud *et al* [47]	Randomised, double blind, monocentre	OC 2 weeks	72	67 (48/72)	74 (42/57)	40 (6/15)

OC, omeprazole-clarithromycin; RC, ranitidine-clarithromycin.

Table 6 Impact of clarithromycin resistance on the eradication of Helicobacter pylori with triple therapies comprised of omeprazole or pantoprazole-clarithromycin-amoxicillin (OCA, PCA)

Reference	Type of study	Type of treatment and duration	No of patients	Eradication (%)		
				Overall	Susceptible	Resistant
Wurzer *et al* [49]	Randomised, double blind, multicentre, MIC centralised	O*CA 10 days	106	90 (95/106)	92 (92/100)	50 (3/6)
Mégraud *et al* [10]	Randomised, double blind, multicentre, MIC centralised	OCA 7 days	118	96 (113/118)	96 (111/116)	100 (2/2)
Lamouliatte *et al* [50]	Randomised, double blind, multicentre, MIC centralised	PCA 7 days	70	80 (56/70)	86 (56/65)	0 (0/5)

O*, omeprazole 20 mg/day; MIC, minimum inhibitory concentration.

synergistically with clarithromycin, as has been shown in vitro.[48]

CLARITHROMYCIN RESISTANCE IN PPI BASED TRIPLE THERAPIES

In the first multicentre study performed, the ACT-10 study,[49] the combination omeprazole-amoxycillin-clarithromycin was given for 10 days. There were only six clarithromycin resistant strains, and only half were eradicated compared with 92% of clarithromycin susceptible strains (table 6). In contrast, in the MACH2 study the two clarithromycin resistant strains were eradicated.

A multicentre study, carried out in southwest France, evaluated pantoprazole instead of omeprazole. None of the five strains resistant to clarithromycin were eradicated compared with 86% of susceptible strains[50] (table 6).

Using the omeprazole-clarithromycin-metronidazole (OCM) combination, in the MACH2 study, four of six (67%) clarithromycin resistant strains were eradicated compared with 98 of 108 (91%) clarithromycin susceptible ones.[10]

Current data are too scarce to draw definitive conclusions on the impact of clarithromycin resistance. However, the high level reported and the lack of reversibility suggest that it could become a major factor in treatment failure if its use increases in the future.

Conclusions

The impact of *H pylori* resistance to clarithromycin and metronidazole is not yet critical because the rate of resistance to clarithromycin is still limited and resistance to metronidazole can be partly overcome. Furthermore, by using a combination of the two antibiotics, one is still effective when resistance to the other exists. However, it is of great importance to monitor this resistance and to find new active compounds for the treatment of *H pylori* infection as problems are already occurring when strains are resistant to both clarithromycin and metronidazole.

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