REVIEW
ΑΝΑΣΚΟΠΗΣΗ

ARCHIVES OF HELLENIC MEDICINE 2003, 20(6):654–661
ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2003, 20(6):654–661

Helicobacter pylori first step eradication therapy. Is it really so simple?

A critical review

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Πρώτο βήμα στη θεραπεία εκρίζωσης του ελικοβακτηριδίου του πυλωρού. Είναι πράγματι τόσο απλό; Μια κριτική προσέγγιση

Περίληψη στο τέλος του άρθρου

Helicobacter pylori **(Hp) has been incriminated in many peptic lesions, over recent years. The eradication of Hp is therefore crucial and effective treatment is considered that with a high eradication yield and a low resistance rate outcome. Combined first step therapies with an antisecretory component and two antibiotics are currently employed to meet the above criteria. The antisecretory component should be a proton pump inhibitor (PPI) or ranitidine bismuth citrate (RBC) prescribed twice daily. Among the antibiotics clarithromycin (CLA) forms the basis of current treatment schemes, usually in combination with amoxycillin (AMO) or metronidazole (MET). The duration of treatment is between seven and ten days. Patient compliance or Hp strains resistant to antibiotics influence the Hp eradication yield. Primary or secondary resistance mainly to MET and less frequently to CLA are important causes of treatment failure. In areas with high MET resistance, physicians can overcome the problem through prescribing either the RBC based regimen (RBC+CLA+MET) or the combination of PPI, CLA and AMO or finally the bismuth based quadruple therapy.**

Key words

Eradication therapy
Helicobacter pylori
Resistance
Triple-therapy schemes

Submitted 1.10.2002
Accepted 3.6.2003

1. INTRODUCTION

Helicobacter pylori (Hp) has been implicated in the physical history of peptic ulcer (PU) disease, gastritis, carcinoma and low grade mucosal associated lymphoid tissue (MALT) lymphoma. According to the consensus of recent years, any Hp eradication regimen should achieve an eradication rate yield of over 80% on an intention to treat basis (ITT). It also needs to be tolerated as well as possible by the patient, to have the least possible side effects and, if possible, induce no secondary resistance, in order to be effective.[1-3]

Over the last years many therapeutic regimens for Hp eradication treatment have been applied in Europe and the United States, but not all of them meet the above criteria and in practice only 50% of primary care physicians and gastroenterologists choose regimens with high effectiveness.[4] Hp eradication therapy has been proved cost effective, especially in PU disease; the less hospital readmission there is, the greater are the inpatient costs saved. In the United States the eradication of Hp has been associated with significant cost savings ($537 compared to treatment with omeprazole, OME) alone and $837 compared to ranitidine in the first year) and this is getting greater over time.[5] In addition, rebleeding of a PU becomes less probable after effective treatment has been completed.[6]

The aim of this review is to present the first step of Hp eradication therapy. Additionally, comment is made on factors that influence Hp eradication, such as drug dosage, treatment duration, medication side effects, demographics and underlying disease, with special focus on the issue of Hp resistance.

2. COMBINED THERAPY AGAINST *H. PYLORI*

In clinical practice, monotherapies are no longer used, because of a low eradication rate yield and high resistance rates. Thus, Hp eradication therapy is based on a combination of antibiotics. So far in the United States, the Food and Drug Administration (FDA) has approved only therapeutic schemes containing lansoprazole (LAN) as the proton pump inhibitor (PPI) twice daily, plus amoxycillin (AMO) plus clarithromycin (CLA) in a two-week scheme, as meeting the consensus criteria.[1] On the

other hand, the European Helicobacter Pylori Study Group (Maastricht 1) has suggested the following schemes to meet the necessary criteria, all administered for seven days.[2]

a. PPI b.d., plus metronidazole (MET), 400 mg b.d./ tinidazole (TIN), 250 mg b.d., plus CLA 250 mg b.d.

b. PPI b.d., plus AMO 1 g b.d., plus CLA 500 mg b.d. (advisable when MET resistance is likely)

c. PPI b.d. plus AMO 500 mg t.i.d., plus MET, 400 mg t.i.d. (advisable when CLA resistance is likely).

In accordance with the above consensus, the ideal first step therapy is a triple scheme with two antibiotics and an antisecretory component. A two antibiotics regimen is superior to a single antibiotic, even if increased to three times a day, probably due to their synergistic effect.[7] However, OME 40 mg b.d. + AMO 500 mg b.d. + MET 400 mg has a low eradication rate yield (only 75.8%, on ITT analysis), according to the metronidazole, amoxycillin, clarithromycin, *H. pylori*, 1 week therapy (MACH 1) study.[8] Additionally, in a United Kingdom/Ireland multicenter study, combination of LAN 30 mg b.d. + AMO 1 g b.d. + MET 500 mg b.d. achieves similar results.[9] MET resistance in Greece is high, over 50%, meaning that this scheme should be applyed cautiously. If a particular antibiotic is known to be associated with a high pretherapeutic resistance rate, it would be better to be replaced by anotherone.

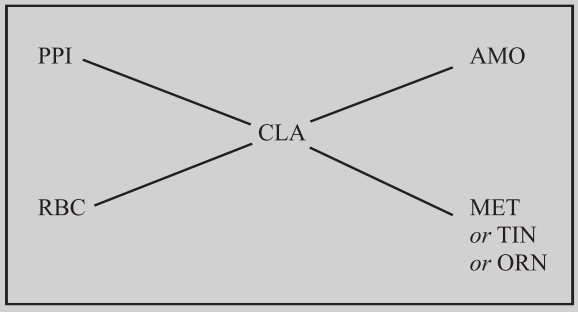
Among those antibiotics used, CLA constitutes the basis of eradication therapy. A summary of triple eradication schemes based on CLA is shown in table 1. The optimal dose is 500 mg b.d., which seems more effective than 250 mg b.d. on both ITT (88.3% vs 86.7%) and PP analysis respectively (89.5% vs 86.6%) (P<0.0001).[10] The proposed scheme is depicted in figure 1 where CLA could be combined with either AMO or MET. A combination of AMO plus CLA may have an additive outcome because the eradication result is that of two dual co-administered therapies. Synergy is the possible mechanism in schemes in which MET is involved.[11] Other authors used ornidazole (ORN) or TIN instead of MET with comparable eradication rates.[12] The antisecretory part of medication should be either a PPI or ranitidine bismuth citrate (RBC). Thus the PPI could be either OME or LAN or the pantoprazole (PAN) or the recently introduced rabeprazole (RAB).[9,13–16]

In a recent meta-analysis, the combination of OME 20 mg b.d. + CLA 500 mg b.d. + AMO 1 g b.d. seems superior to LAN 30 mg b.d. + CLA 500 mg b.d. + AMO 1 g b.d. or PAN 40 mg b.d. + CLA 500 mg b.d. + AMO 1 g b.d. (82.7% vs 76.8% vs 76.7%),[12] but this is based on pooling data and is not a comparative study. With regard to which of the PPIs is the most effective the evidence is inconclusive, but when OME is the PPI component, MET seems to be superior to AMO with regard to the eradication rate (86% vs 79%).[17] Finally, in the classic MACH 1 study no statistical difference was observed between AMO and MET (90.6% vs 89.7%) regarding the eradication rate.

Table 1. Summary of data with 1 week clarithromycin triple eradication therapy.

Regimen	No of treatment arms n/N		ITT (%)	Range (%)
RBC+CLA+AMO	9	427/521	82	39–94
OME+CLA+AMO	51	2886/3489	82.7	50–98
LAN+CLA+AMO	23	975/1270	76.8	24–92
PAN+CLA+AMO	11	541/705	76.7	24–92
RBC+CLA+MET	10	702/791	88.7	82–98
OME+CLA+MET	42	2003/2414	83	45–100
LAN+CLA+MET	17	801/924	86.7	68–100
PAN+CLA+MET	10	673/806	83.5	63–100
RBC+CLA+TIN	4	165/198	83.3	73–91
OME+CLA+TIN	27	1289/1496	86.2	54–97
LAN+CLA+TIN	5	225/293	76.8	55–93
PAN+CLA+TIN	1	48/56	85.7	–

AMO: Amoxycillin; CLA: Clarithromycin; LAN: Lansoprazole; MET: Metronidazole; OME: Omeprazole; PAN: Pantoprazole; RBC: Ranitidine bismuth citrate; TIN: Tinidazole; ITT: Intention to treat. Adapted from Pipkin et al[12]



PPI: Proton pump inhibitor; AMO: Amoxycillin; CLA: Clarithromycin; MET: Metronidazole; RBC: Ranitidine bismuth citrate; TIN: Tinidazole; ORN: Ornidazole

Figure 1. *Helicobacter pylori* triple scheme eradication therapy.

RBC in a one-week regimen is another effective option, particularly when there are Hp strains resistant to MET prior to therapy. RBC 400 mg b.d. + CLA 500 mg b.d. + AMO 1 g b.d or MET 500 mg b.d. are two other possible options, and on ITT analysis the eradication rates are 82% and 88.7%, respectively[12] (tab. 1). A significant superiority of effectiveness of the RBC+CLA+nitroimidazole over the RBC+CLA+AMO scheme has been reported.[18] There have been few studies comparing PPIs with RBC, none suggesting statistically significant effectiveness of the former over the latter. A few years ago comparison of RAN 400 mg b.d. + CLA 500 mg b.d. + MET 500 mg b.d. with OME 20 mg b.d. + CLA 500 mg b.d. + MET 500 mg b.d. showed the first scheme superior to the second with regard to Hp eradication, on an ITT analysis (87% vs 52%) (P<0.003).[19] However, in a recent meta-analysis no significant effectiveness of RBC over PPIs has been shown,[20] although in areas with a known high MET resistance, the RBC schemes are especially beneficial (tab. 1).

3. FACTORS WHICH INFLUENCE *H. PYLORI* ERADICATION THERAPY

There are many factors affecting the final optimal therapeutic result the most important of which are patient compliance and bacterial resistance against antibiotics.[21] Patient compliance depends on duration of therapy, side effects of medication and total daily pills number. Interestingly, an underlying lesion such as PU presents a different eradication outcome compared to non-ulcer dyspepsia (NUD).[22] Demographic factors also play a role and social factors such as smoking, alcohol consumption and food habits may also affect the outcome.[23]

3.1. Dosage

A few years ago, it was proposed that shorter courses of OME, in a dose of only 20 mg a day plus CLA plus MET, could be as efficacious against *H. pylori*, as longer duration courses.[24] However a recent meta-analysis reports that OME 20 mg b.d. is superior to 20 mg o.d. and the same seems to apply to LAN 30 mg b.d. vs o.d.[25] PAN is recommended at a dose of 40 mg b.d.,[12] RAB at 20 mg b.d.[15] and ranitidine bismuth salts at 400 mg b.d.[12] There are many options, with regard to the antibiotics which can be used, among which, AMO 1 g b.d., CLA 500 mg b.d., MET 500 mg b.d. in Greece or 400 mg b.d. elsewhere, seem to be the most efficacious.[12] TIN or ORN, 500 b.d., can be substituted for MET, providing similar eradication rate yield.[23,26]

3.2. Duration

Bazzoli has suggested a seven-day regimen[24] but the FDA has so far approved the two weeks scheme. It should not be forgotten that the longer the duration of therapy, the poorer the patient compliance is.[27] Lamouliatte on the other hand has suggested that eradication rates would be higher if duration of therapy was increased from seven to ten days.[28] Although many physicians prefer the short course, the optimal treatment duration is still to be found and it is necessary to balance between the optimal therapy duration and the patient compliance.

3.3. Side effects

In general, side effects of treatment are mild, as reported in the majority of studies. The most common are diarrhea or loose stools, taste disturbances, headache, nausea, abnormal liver function tests, black tongue or black feces. Only a very small percentage of patients (2.5%) discontinued treatment because of side effects.[8,9,17,29] Among patients who discontinued, diarrhea was the most common reason. Some rare side effects have also been reported including disturbances of cardiac rhythm, heart failure, pneumonia, gastrointestinal tract carcinoma. However, these side effects have been considered unrelated to the study treatment by the treating clinicians.

3.4. Demographic factors

Several studies have shown that different ethnic groups in the same country, present different eradication rates on the same treatment. For example, the Turkish population in Germany presented poor eradication efficacy

on ITT analysis, of only 60% of that of the native population,[30] which means that either Hp strains with different virulence exist or the host immune factors do not act in the same way among different ethnic groups. Another explanation is that ethnic groups may present variable Cag A (+) strains prevalence, as well as primary antibiotic resistance.

3.5. The underlying lesion

In various studies, the Hp eradication rate is considered to be around 80% for PU patients. However, the rates vary between patients with gastric or duodenal ulcer or NUD. Patients with duodenal ulcer present higher Hp eradication rates than patients suffering from gastric ulcer or NUD[22] although at this point there seems to be a controversy, as some studies suggest high efficacy of the triple scheme for patients with gastric ulcer or NUD.[31,32] A possible explanation could be obscure PUs among patients in the studies. A recent meta-analysis suggests that eradication of Hp is higher in PU than NUD only if the 7-day PPI based triple regimen is applied. The 7-day RBC based triple scheme provides equal effectiveness.[22] Cytotoxin associated gene A (+) (Cag A), vacuolating cytotoxin A (Vac A) s1 strains are more susceptible to eradication treatment, than Cag A (-), Vac A s2.[33,34] Among gastritis typer, pangastritis and antrum predominant gastritis present more favorable eradication result compared with lymphoid follicular one.[32]

3.6. Resistance

Primary and secondary resistance of Hp to antibiotics appears to be the major reason for treatment failure. Primary resistance is resistance that exists before treatment and secondary resistance of Hp to antibiotics is defined as that acquired post-treatment. Among the antibiotics currently in use, MET and CLA are of primary concern, because of the resistance developed to them. No primary or secondary resistance of Hp to AMO has so far been observed. The prevalence of MET resistance in Europe is increasing and varies between countries from 7% to 49% while in Greece, primary MET resistance is over 50%[35] and in Asia and Central Africa is as high as 84%.[36] Therapeutic schemes with MET achieve only a 57% eradication rate when primary MET resistance preexists whereas in MET sensitive patients the rate is 98%.[35] The MACH 2 study has reported similar results.[29] If primary resistance to both MET and CLA exist the results of eradication therapy are impressively negative, the score rate being zero.[29,36] The effect of MET resistance on eradication outcome, as part of a triple scheme PPI+CLA+MET, has been studied extensively, but there is still heterogeneity in results as shown in table 2.[16,29,36–41] In order to estimate MET resistance *in vitro*, various antibiotic susceptibility tests have been applied that are not similar[42] and may partly explain these results, along with the lack of uniformity in study design.

The role of the MACH 2 study[29] in elucidating the impact of OME and Hp resistance on treatment outcome has been outstanding. According to this study, MET resistance can be overcome, by replacing MET with AMO in the triple regimen therapy. Another point of this study is that the addition of OME 20 mg daily to the therapeutic scheme reduces primary resistance and may decrease the risk of secondary resistance, compared with schemes containing only two antibiotics. The explanation is that OME provides the optimal pH for antibiotics to become more potent.[43]

Table 2. PPI-CLA-MET/TIN: Metronidazole resistance impact.

Study	Regimen	N	Antibiotic susceptibility test	MET sensitivity		MET resistance	
Peitz et al[37]	OME+CLA+MET 7	87	E-test	100	(49/49)	81.6	(31/38)
Bazzoli et al[38]	OME+CLA+TIN 7	22	E-test	100	(18/18)	75	(3/4)
UK/Ireland[16]	LAN+CLA+MET 7	78	E-test	94.5	(69/73)	76	(19/25)
Buckley et al[36]	OME+CLA+MET 7*	84	Agar dilution	98.2	(55/56)	57.1	(16/28)
Georgopoulos et al[39]	OME+CLA+MET 7**	41	Agar dilution	100	(24/24)	58.3	(10/17)
Lerang et al[41]	OME+CLA+MET 10	64	E-test	94	(45/48)	94	(17/18)
MACH 2[29]	OME+CLA+MET 7	114	Agar dilution	95	(77/81)	76	(25/33)
Kist et al[40]	PAN+CLA+MET 7, 14	188	E-test	90	(115/128)	74	(40/60)

*OME: 20 mg × 1, **CLA: 500 mg × 2

CLA: Clarithromycin; LAN: Lansoprazole; MET: Metronidazole; OME: Omeprazole; PAN: Pantoprazole; TIN: Tinidazole

There are limited data regarding secondary MET resistance in the literature. According to the MACH 2 study, resistance is higher in a regimen with no OME involvement[29] but the number of these patients in the study was low and the results not statistically significant. It is interesting that MET resistance induces secondary CLA resistance as shown in figure 2. In accordance to this histogram, in Greece where the MET resistance rate is about 50%, the acquired CLA resistance is expected to be around 15%. Comparing Greek and Irish studies with similar MET resistance rates (fig. 3), it can be seen that it is crucial to employ double CLA dosage, 500 mg, to overcome the acquired CLA resistance.

If the local rate of MET resistance is high or there are patients with possible MET resistant strains, then schemes containing a PPI+CLA+AMO, or RBC instead of PPI, or quadruple schemes should be applied. A few studies have examined the effect of primary antibiotic resistance on the efficacy of RBC-based triple therapies (RBC+CLA+MET). It is suggested that the dual mode of action of RBC, as well as the strong synergism with CLA may help to overcome antibiotic resistance.[44,45] In cases of resistance to both CLA and MET there are two options. The first is Hp culture testing with *in vitro* antibiotic sensitivity.[1] The second is application of quadruple schemes, such as PPI+bismuth salts+MET+tetracycline, which are not influenced to the same extend, by MET resistance. However, the quadruple scheme should be reserved as the final option in cases of Hp eradication failure.[46,47]

Primary CLA resistance, which has a low prevalence in Europe, does not contribute significantly to treatment failure of the triple scheme OME 20 mg o.d. + CLA 250 mg b.d. + MET 400 mg b.d.[36] An uncontrolled Spanish study showed that CLA resistance significantly impaired the effectiveness of the combination of LAN+AMO+CLA.[48] The 80% efficacy goal would be difficult to be achieved in areas with high (>10%) primary CLA resistance if the currently recommended PPI-triple therapies are employed.[41] In the MACH 2 study the overall primary resistance was low (3%). Secondary resistance to CLA does develop in patients treated with PPI+CLA+AMO or MET, formerly sensitive to the above antibiotics, but is still low (7–9%), when AMO cotherapy is used and the dosage of CLA is 1 g a day.[49] Specifically, CLA resistance develops post-treatment due to MET, in areas with high MET resistance.[36] This is potentially worrying, because it leads to dual resistance and ultimately to a low eradication rate yield. To date, no data have been

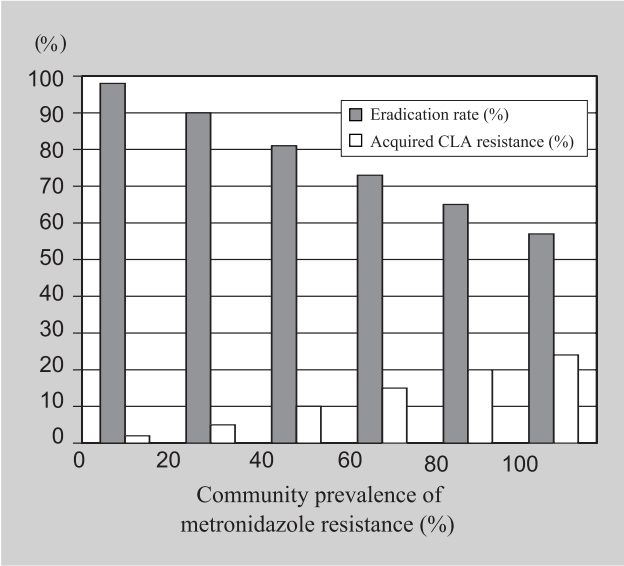


Figure 2. Metronidazole resistance and acquisition of secondary clarithromycin resistance. The postulated eradication rates are calculated on the basis that 98.2% of metronidazole-sensitive strains and 57.1% of metronidazole-resistant strains are eradicated. Adapted from Buckley et al.[36]

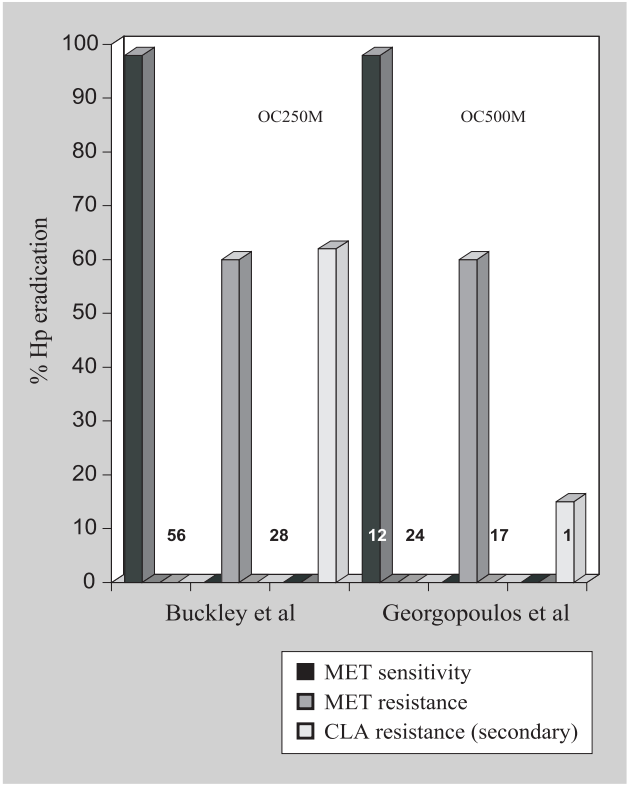


Figure 3. Impact of clarithromycin dosage on secondary clarithromycin resistance. Comparison of two studies. Adapted from Buckley et al[36] and Georgopoulos et al.[39] OC250M: Omeprazole+Clarithromycin 250 mg+Metronidazole. OC500M: Omeprazole+Clarithromycin 500 mg+Metronidazole.

reported with regard to resistance of the scheme RBC+CLA+AMO.

4. CONCLUSIONS

Triple schemes containing PPI or RBC+CLA+AMO or MET are necessary to achieve high eradication rates. The optimal treatment duration with the triple regimen of PPI+CLA+AMO is still to be determined (7 days or longer). Side effects of triple schemes are mild and do not affect the compliance of patients. Hp is eradicated more easily in PU than in NUD lesions. Resistance to the antibiotics MET or CLA is a very important factor of treatment failure. Double daily dosage of CLA and PPI or RBC or a quadruple regimen should be used to overcome resistant Hp strains.

ΠΕΡΙΛΗΨΗ

Πρώτο βήμα στη θεραπεία εκρίζωσης του ελικοβακτηριδίου του πυλωρού. Είναι πράγματι τόσο απλό; Μια κριτική προσέγγιση

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Αρχεία Ελληνικής Ιατρικής 2003, 20(6):654–661

Το ελικοβακτηρίδιο του πυλωρού έχει ενοχοποιηθεί σε πολλές παθήσεις του στομάχου τα τελευταία χρόνια. Η εκρίζωση του βακτηριδίου αυτού έχει, επομένως, μεγάλη σημασία. Μια αποτελεσματική θεραπεία είναι αυτή που συνδυάζει υψηλό ποσοστό εκρίζωσης και χαμηλό ποσοστό αντοχής. Συνδυασμένες θεραπείες με έναν παράγοντα καταστολής του οξέος (αντιεκκριτικό) και δύο αντιβιοτικά φαίνεται ότι εκπληρώνουν τις ανωτέρω προϋποθέσεις και αποτελούν το πρώτο βήμα στην προσπάθεια εκρίζωσης. Ο αντιεκκριτικός παράγοντας πρέπει να είναι ένας αναστολέας της αντλίας πρωτονίων ή ο συνδυασμός ρανιτιδίνης-κιτρικού βισμουθίου. Και για τις δύο περιπτώσεις προτείνεται η χορήγησή τους δύο φορές την ημέρα. Από τα αντιβιοτικά, η κλαριθρομυκίνη αποτελεί τον ακρογωνιαίο λίθο της θεραπείας πρόσφατα. Η συνιστώμενη δόση είναι 500 mg δύο φορές την ημέρα, η οποία, επιπλέον, αποτρέπει την ανάπτυξη δευτερογενούς αντοχής στη μετρονιδαζόλη. Η διάρκεια της αγωγής ανέρχεται σε 7–10 ημέρες. Η συμμόρφωση των ασθενών στη θεραπεία και η αντοχή του μικροβίου στα αντιβιοτικά επηρεάζουν το αποτέλεσμα της εκρίζωσης. Πρωτογενής ή δευτερογενής αντοχή, κύρια στη μετρονιδαζόλη αλλά και στην κλαριθρομυκίνη, αποτελούν σημαντικές αιτίες αποτυχίας της θεραπείας. Σε περιοχές με υψηλή αντοχή στη μετρονιδαζόλη, οι γιατροί μπορούν να ξεπεράσουν το πρόβλημα συμπεριλαμβάνοντας στα σχήματα τη ρανιτιδίνη-κιτρικό βισμούθιο ή αναστολέα της αντλίας πρωτονίων με κλαριθρομυκίνη και αμοξικιλίνη ή το τετραπλό σχήμα εκρίζωσης με βισμούθιο.

Λέξεις ευρετηρίου: Ανθεκτικότητα, Ελικοβακτηρίδιο του πυλωρού, Θεραπεία εκρίζωσης, Τριπλά θεραπευτικά σχήματα

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