Table 1.: Recent studies on positive associations of *Helicobacter pylori* infection with extra-gastric disease

[1]Population-based retrospective cohort study; [2]Prospective cohort study; [3]Meta-analysis; [4]Population-based prospective cohort study; [5]Systematic review; [6]Randomised controlled trial

Disease	Number of Patients	References
Cardiovascular diseases		
Acute coronary syndrome	85375[1]	445
	433[2]	446
	21829[3]	447
	300[2]	448
	9953[4]	449
Ischemic stroke	86660[1]	450
Metabolic disorders		
Metabolic syndrome	3578[2]	451
Insulin resistance	370[2]	452
	2120[5]	453
Diabetes mellitus	1285[2]	454
	429[2]	455
	14080[3]	456
Neurodegenerative diseases		
Alzheimer's disease	263[2]	87
	53[2]	88
Ocular Alzheimer's disease	156[2]	457
Idiopathic Parkinson's disease	106[2]	458
	272[2]	[16]
	30[6]	459
Multiple Sclerosis	64[2]	460
Haematological diseases		
IDA	151[2]	461
	311[2]	74
	956[3]	75
ITP	85[6]	462
	95[2]	463
	244[2]	81
Other		
Migraine	903[3]	464

Chronic urticaria	200[2]	[465]
Rosacea	180[2]	[466]

Table 2.: Recent studies on negative associations of *Helicobacter pylori* infection with extra-gastric disease
[1]Population-based prospective cohort study; [2]Meta-analysis; [3]Prospective cohort study; [4] Randomised controlled trial; [5]Retrospective cohort study

Disease	**Number of Patients**	**References**
Cardiovascular diseases		
Acute coronary syndrome	9953[1]	[449]
Stroke	166041[2]	[467]
Neurodegenerative diseases		
Multiple Sclerosis	113[3] 849[3]	[468] [469]
Haematological diseases		
IDA	200[3] 127[3]	[470] [471]
Other		
Obesity	1558[4]	[19]
Asthma	9492[5]	[472]
IBD	1268[5] 9163[2] 80789[2]	[473] [474] [475]

Table 3. Expected rate of dual resistant *H. pylori* strains in a population, depending on previously known clarithromycin and metronidazole resistance.
Populations expectations should always be correlated individually with susceptibility testing (wherever possible) or at the least with patient´s antibiotic history.

Metronidazole resistance	Clarithromycin resistance	Dual resistance
50%	15%	7.5%
	20%	10%
	30%	**15%**
	40%	20%
	50%	25%
40%	15%	6%
	20%	8%
	30%	12%
	40%	**16%**
	50%	20%
30%	15%	4.5%
	20%	6%
	30%	9%
	40%	12%
	50%	**15%**
20%	15%	3%
	20%	4%
	30%	6%
	40%	8%
	50%	10%

Table 4. Example of efficacy of clarithromycin-containing regimens for an individual patient, based on predicted resistance to clarithromycin and metronidazole1

Dark grey boxes denote successful eradication rates (>90%)

Antimicrobial prediction	**7-day triple therapy**	**14-day triple therapy**	**10-day sequential therapy**	**14-day sequential therapy**	**10-day concomitant therapy**	**14-day concomitant therapy**	**14-day bismuth quadruple therapy**
Clarithromycin and metronidazole susceptible	**94%**	**97%**	**95%**	**98%**	**94%**	**97%**	**99%**
Clarithromycin resistant-metronidazole susceptible	<20%	50%	80%	88%	**94%**	**97%**	**99%**
Clarithromycin susceptible-metronidazole resistant	**94%**	**97%**	75%	75%	**94%**	**97%**	**95%**
Clarithromycin and metronidazole resistant	<20%	50%	<20%	<20%	<25%	<50%	**95%**

Table 5. Reported cure rates for 10-day concomitant and sequential therapy against clarithromycin-resistant and metronidazole-susceptible *H. pylori* strains in head-to-head comparative trials.

	Sequential	**Concomitant**
Georgopoulos, Greece [189], 2014	11/14 (79%)	11/14 (79%)
Huang, China, 2012[476]	3/5 (60%)	3/3 (100%)
Molina-Infante, Spain, 2012[477]	3/4 (75%)	5/5 (100%)
Wu, Thailand 2010[478]	4/7 (57%)	3/4 (75%)
Mean	**21/30 (70%)**	**22/26 (84%)**

Table 6. Cumulative cure rates for concomitant and sequential therapy against clarithromycin-resistant and metronidazole-susceptible *H. pylori* strains in recent literature (inverse chronological order).

Several studies[22-27] were excluded as they reported efficacy rates of sequential therapy against either clarithromycin susceptible- or resistant-strains, but did not analyze metronidazole susceptibility

	Sequential	**Concomitant**	**Treatment duration (days)**
Zhou, China, 2014[479]	8/9 (88%)	-	10
Georgopoulos, Greece, 2014[189]	11/14 (79%)	11/14 (79%)	10
Morse, Canada, 2013[480]	0/1 (100%)	-	10
Molina-Infante, Spain, 2013[188]	-	5/5 (100%)	14
Georgopoulos, Greece, 2013[481]	-	13/15 (87%)	10
Liou, Taiwan, 2013[214]	10/14 (71%)	-	14
Liou, Taiwan, 2013[214]	7/10 (70%)	-	10
Huang, China, 2012[476]	3/5 (60%)	3/3 (100%)	10
Molina-Infante, Spain, 2012[477]	3/4 (75%)	5/5 (100%)	10
Wu, Thailand, 2010[478]	4/7 (57%)	3/4 (75%)	10
Bontems, France, 2011[482]	9/16 (56%)	-	10
Romano, Italy, 2010[483]	9/12 (75%)	-	10
Vaira, Italy, 2007[484]	8/9 (88%)	-	10
Zullo, Italy, 2003[485]	7/9 (78%)	-	10
Mean	**79/110 (71%)**	**40/46 (87%)**	

Table 7. Reported cure rates for **10-day concomitant and sequential therapy against clarithromycin-susceptible and metronidazole-resistant** *H. pylori* strains in head-to-head comparative trials.

	Sequential	**Concomitant**
Georgopoulos, Greece, 2014[189]	21/28 (75%)	21/21 (100%)
Huang, China, 2012[476]	14/18 (78%)	16/16 (100%)
Wu, Thailand 2010[478]	27/30 (90%)	24/26 (92%)
Mean	**62/76 (81%)**	**61/63 (97%)**

Table 8. Cumulative cure rates for **concomitant and sequential therapy** against **clarithromycin-susceptible and metronidazole-resistant** *H. pylori* strains in recent literature (inverse chronological order).

	Sequential	**Concomitant**	**Treatment duration (days)**
Zhou, China, 2014[479]	41/47 (87%)	-	10
Georgopoulos, Greece, 2014[189]	21/28 (75%)	21/21 (100%)	10
Morse, Canada, 2013[480]	4/4 (100%)	-	10
Molina-Infante, Spain, 2013[188]	-	8/8 (100%)	14
Georgopoulos, Greece, 2013[481]	-	25/25 (100%)	10
Liou, Taiwan, 2013[16]	30/34 (88%)	-	14
Liou, Taiwan, 2013[16]	32/44(73%)	-	10
Huang, China, 2012[8]	14/18 (78%)	16/16 (100%)	10
Molina-Infante, Spain, 2012[10]	-	8/8 (100%)	10
Wu, Thailand, 2010[478]	27/30 (90%)	24/26 (92%)	10
Bontems, France, 2011[482]	14/16 (88%)	-	10
Romano, Italy, 2010[483]	13/14 (92%)	-	10
Kalach, France, 2008[486]	4/5 (80%)	-	10
Vaira, Italy, 2007[484]	34/35 (97%)	-	10
Zullo, Italy, 2003[485]	34/36 (94%)	-	10
Mean	**268/311 (86%)**	**102/104 (98%)**	

Table 9. Reported cure rates for **10-day concomitant and sequential therapy** against **dual clarithromycin- and metronidazole-resistant** *H. pylori* strains in head-to-head comparative trials.

	Sequential	Concomitant
Georgopoulos, Greece, 2014[189]	2/5 (40%)	7/9 (78%)
Huang, China, 2012[476]	2/4 (50%)	2/2 (100%)
Molina-Infante, Spain, 2012[477]	3/5 (60%)	3/4 (75%)
Wu, Thailand, 2010[478]	1/3 (33%)	3/4 (75%)
Mean	**8/17 (47%)**	**15/19 (79%)**

Table 10. Cumulative cure rates for **concomitant and sequential therapy** against **dual clarithromycin- and metronidazole-resistant** *H. pylori* strains in recent literature (inverse chronological order).

	Sequential	Concomitant	Treatment duration (days)
Zhou, China, 2014[479]	17/37 (46%)	-	10
Georgopoulos, Greece, 2014[189]	2/5 (40%)	7/9 (78%)	10
Morse, Canada, 2013[480]	1/1 (100%)	-	10
Molina-Infante, Spain, 2013[188]	-	3/3 (100%)	14
Georgopoulos, Greece, 2013[481]	-	7/10 (70%)	10
Liou, Taiwan, 2013[214]	3/8 (37%)	-	14
Huang, China, 2012[476]	2/4 (50%)	2/2 (100%)	10
Molina-Infante, Spain, 2012[477]	3/5 (60%)	3/4 (75%)	10
Wu, Thailand, 2010[478]	1/3 (33%)	3/4 (75%)	10
Romano, Italy, 2010[483]	0/3 (0%)	-	10
Kalach, France 2008[486]	1/1 (100%)	-	10
Vaira, Italy, 2007[484]	0/4 (0%)	-	10
Zullo, Italy, 2003[485]	8/10 (80%)	-	10
Mean	**38/81 (47%)**	**25/32 (78%)**	

Table 11. Studies evaluating the efficacy of a third-line combination of a PPI, amoxicillin, and levofloxacin for the eradication of *H. pylori* infection after two eradication failures.

Author	Year of publication	Number of patients	Previous (failed) treatments	Duration(days)	Eradication¶ (%)
Gatta et al[270]	2005	151	1st: PPI+C+A or M 2nd: PPI+C+A or M; Q		76
Gisbert et al[271]	2006	100	1st: PPI+C+A 2nd: Q	10	60
Gisbert et al[272]	2006	20	1st: PPI+C+A 2nd: Q	10	85
Rokkas et al[273]	2009	30	1st: PPI+C+A 2nd: Q	10	70
Gisbert et al[274]	2012	200	1st: PPI+C+A 2nd: Q	10	68

¶Intention-to-treat.

PPI: proton pump inhibitor; C: clarithromycin; M: metronidazole; A: amoxicillin; Q: bismuth-containing quadruple therapy (PPI, bismuth, tetracycline and M).

Table 12. Studies evaluating the efficacy of a combination of a PPI, amoxicillin, levofloxacin and bismuth for the eradication of *H. pylori* infection.

Author & publication year	Country	Treatment order	Duration (days)	Eradication rate by intention-to-treat n/N (%)
Bago 2007[297]	Croatia	First	7	57/66 (86%)
Gao 2010[298]	China	First	10	60/72 (83%)
Hsu 2008[299]	Taiwan	Third	10	31/37 (84%)
Liao 2013[296]	China	First	14	70/80 (87.5%)
Yee 2007[300]	China	≥ Second	7	37/51 (73%)
Gisbert[284]	Spain	Second	14	180/200 (90%)

Table 13. *Studies evaluating the efficacy of a third-line combination of a PPI, amoxicillin, and levofloxacin for the eradication of H. pylori infection after two eradication failures.*

Author and Reference	***Year of publication***	***Number of patients***	***Previous (failed) treatments***	***Duration(days)***	***Eradication¶ (%)***
Gatta et al[270]	*2005*	*151*	*1st: PPI+C+A or M* *2nd: PPI+C+A or M; Q*		*76*
Gisbert et al[271]	*2006*	*100*	*1st: PPI+C+A* *2nd: Q*	*10*	*60*
Gisbert et al[272]	*2006*	*20*	*1st: PPI+C+A* *2nd: Q*	*10*	*85*
Rokkas et al[273]	*2009*	*30*	*1st: PPI+C+A* *2nd: Q*	*10*	*70*
Gisbert et al[274]	*2012*	*200*	*1st: PPI+C+A* *2nd: Q*	*10*	*68*

¶*Intention-to-treat.*

PPI: proton pump inhibitor; C: clarithromycin; M: metronidazole; A: amoxicillin; Q: bismuth-containing quadruple therapy (PPI, bismuth, tetracycline and M).