

1.Title

**Usefulness of Five Antimicrobial Susceptibility Tests for Eradication of
H. pylori
(Subsequent report)**

The 29th Annual Meeting of the Japanese Society for
Helicobacter Research
(June 30, 2023)

Araki Clinic of Proctology
Osaka Sakai, Japan
Tsuneo Araki

2.COI Disclosure

Nothing to disclose

The 29th Annual Meeting of the Japanese society for
Helicobacter Research
(June 30, 2023)

3.Purpose

To examine the usefulness of five susceptibility testing for selection of appropriate drug regimen for eradication of *H. pylori*.

4. Subjects

History of eradication	number
No (initial cases)	87
Yes(re-eradication cases)	10**
total	97**

1) **97 cases underwent antibiotic eradication for H. pylori (from August 2013~December 2019).**

2) **In the group of re-eradication cases, the number of patients by number of previous eradication were

six patients with one, two with two, one with three, one with four.

3) ****In this group, there is one person who was tested twice, so the actual person-number is 96.**

4) Mean 54 years, range 31-78,

5) **94 females and 3 males,**

6) Mean body weight 54.4 ± 10.1 kg, range 29.4-94.4 kg

5. Methods

1. Gastric mucosa was collected **from two locations** (the pylorus and upper gastric body of great curvature) on endoscopy at Mimihara General Hospital (Dr. Masahiro Okada)
2. Cultured on Nissui HP agar medium microaerophilically for 1 week.
H. pylori was identified on urease activity test and Gram stain.
3. **MIC was measured using the agar plate dilution method.**

6.MIC break point criteria

Antibacterial agent	MIC break-point (μg/ml)		
	S (sensitive)	I (intermediate)	R (resistant)
CAM* ¹	≤ 0.25	0.5	≥ 1
AMPC* ²	≤ 0.03	Uncertain	Uncertain
MNZ* ³	≤ 8	Uncertain	≥ 16
MINO* ⁴	< 1		≥ 1
STFX* ⁵	< 1		≥ 1

source

*1. CLSI (clinical and laboratory standard institute), The Japanese Society for Chemotherapy, June 2006

*2 .The Japanese Society for Chemotherapy, June 2006

*3. EUCAST (European committee on antimicrobial susceptibility testing)

*4. Helicobacter Research vol.25 no2. 2021 p34-43, Takahisa Huruta

Japanese Journal of Helicobacter Reach Vol24.no1. 2022 p65-69, Huruta et al

*5. Helicobacter Research vol.18 no2. 2014 (Murakami K et al, 2013)

7. Antimicrobial selection criteria

(1) To adopt sensitive antimicrobial and no unsensitive ones.

For the same sensitivity test, select the drug with the lower MIC.

(2) If all five species are sensitive, AMPC and CAM are preferred.

Next, MNZ is preferred.

(3) If the MIC of MINO is the same or lower than that of STFX, preference is given to MINO. The reason is low cost.

(4) The combination of AMPC and MINO is accepted. (There were 8 cases.)

8.Type of gastric acid secretion inhibitors and penicillin excretion-inhibitor

Lansoprazole: 60mg/2divide/10 days as PPI was used to all 49 patients in the first term (2014.1.23-2015.4.10),

Vonoprazan: 40 mg/2 divide/7-10 days was used to 46 patients in the second term (2015.4.25-2020.2.18)

In the second term, when AMPC was selected, **probenecid** 1000 mg/2 divide/7 days, a penicillin excretion inhibitor, was also used.

9.Method of confirming eradication

method	Product Name	number
Stool pylori antigen test	Testmate Pylori Antigen EIA (Wakamoto Seiyaku, Japan)	86
Urea breath test	UBIT tablet 100mg (Otsuka Pharmaceutical)	8
Antibody test		1
total		95

Timing: after 8 weeks of eradication

Of these, one patient had both a stool Pylori antigen test and a urea breath test.)

10. Statistical processing method

1) Patient data were compiled using FileMaker pro (v.8), and Windows Excel 2016 was used for T-test.

2) When one of the observed frequencies in the χ -square test had a number less than 5, a P value was obtained using Fisher's direct probability test method.

3) The significant difference test was a one-tailed test, and a significance level of $P < 0.05$ was used.

11.AMPC susceptibility test result

MIC (µg/ml)	≤ 0.03	0.06	0.12	0.25	0.5	Total	number of non-sensitive cases (percentage)	P values
number	80	11	3	2	1	97	17 (18%)	
Initial eradication	74	9	3	1	0	87	13(15%)	0.07
history of eradication	6	2	0	1	1	10	10(4%)	

**Bold numbers indicate non-susceptible cases
Note the variation of MIC in non-sensitive cases.**

12.MINO susceptibility test results

MIC (µg/ml)	≤0.03	0.06	0.12	0.25	0.5	Total (number of non-sensitive cases)	number of non-sensitive cases (percentage)	P value
Number(MINO)	14	22	35	25	1	97	0	
no history of eradication	13	19	30	24	1	87	0	(no difference)
history of eradication	1	3	5	1	0	10	0	

**There were no non-sensitive cases.
However variation in MIC is observed.**

13.STFX susceptibility test results

MIC (μg/ml)	≤ 0.03	0.06	0.12	0.25	0.5	1	Total number	number of non-sensitive cases (percentage)	P value
number (STFX)	45	11	29	9	1	2	97	2(2%)	
Initial eradication	42	10	25	8	1	1	87	1(1%)	0.197
history of eradication	3	1	4	1	0	1	10	1(10%)	

Bold numbers indicate non-susceptible cases

Like MINO, STFX also has a small resistance rate of 2%, and variation in MIC is observed.

14. Comparison for Rate of non-sensitive between initial and past eradication

Antibiotics		Sensitive numbers	Non-sensitive numbers	Ratio of non-sensitive%	P-value initial vs past
AMPC	Initial eradication 87	74	13	29.8	
	Past eradication 10	6	4	40	0.07
	total 97	80	17	17.5	
CAM	Initial eradication	50	37	42.5	
	Past eradication	2	8	80	0.027
	total	52	45	46.4	
MNZ	Initial eradication	75	12	13.8	
	Past eradication	7	3	30	0.183
	total	82	15	15.5	
MINO	Initial eradication	87	0	0	
	Past eradication	10	0	0	No test
	total	97	0	0	
STFX	Initial eradication	86	1	2.3	
	Past eradication	9	1	10	0.197
	total	95	2	2.1	

15. Rates of multiple agent resistance (more than 2 agents)

Number of resistant drugs	Initial eradication	history of eradication	Total
0	33	1	34
1	41	4	45
2	13	4	17
3	0	1	1
Total	87	10	97

In cases of first-time eradication, **15%(13/87)**

In cases with a history of eradication, **50%(5/10)**

P value $\hat{=}$ 0.0178

16. Comparison for Rate of non-sensitive between this report and another one's (in cases of initial eradication)

Antibiotics	Sensitive	Non-sensitive	Ratio of non-sensitive%	P-value
AMPC	74	13	29.8	0.0002
CAM	50	37	42.5	0.3974
MNZ	75	12	13.8	0.0017
MINO	87	0	0	Not tested
STFX	86	1	1.1	0.7540

This report.
Significant differences were found in AMPC and MNZ .

Antibiotics	Sensitive	Non-sensitive	Ratio of non-sensitive %
AMPC*	1798	101	5.3
CAM*	1177	722	38.0
MNZ*	1792	107	5.6
MINO**	147	0	0
STFX**	145	2	1.4

*Current status of drug-resistant *Helicobacter pylori* in Japan: a report on surveillance of resistant bacteria in 2015~2016-2020.J.J.H.R Vol.21.no2

***Helicobacter pylori* Eradication Therapy for Resistant Bacteria 2021J.of H.R. Vol.25no.2

17. Comparison regarding Rate of non-sensitive between this report and another one's (in cases of past eradication)

Antibiotics	Sensitive	Non-sensitive	Ratio of non-sensitive %	P-value
AMPC	6	4	40	0.028
CAM	2	8	80	0.560
MNZ	7	3	30	0.044
MINO	10	0	0	0.957
STFX	9	1	10	0.565

This report.
Significant differences were found in AMPC and MNZ .

Antibiotics	Sensitive	Non-sensitive	Ratio of non-sensitive%
AMPC**	194	26	11.8
CAM*	52	240	82.2
MNZ*	111	183	62.2
MINO**	219	1	0.5
STFX**	203	17	7.7

*Current status of drug-resistant *Helicobacter pylori* in Japan: a report on surveillance of resistant bacteria in 2015~2016-2020.J.J.H.R Vol.21.no2

***Helicobacter pylori* Eradication Therapy for Resistant Bacteria 2021J.of H.R. Vol.25no.2

18. eradication success rate (first time in our clinic)

	result	total number	PPI Usage Examples	VPZ usage Examples	Ratio
Initial eradication 87 cases	success	81	40	41	$81/87 \doteq 0.93$
	failure	3	3	0	$3/87 \doteq 0.03$
	Terminated due to allergy	1	1	0	$1/87 \doteq 0.01$
	No follow-up	2	0	2	$2/87 \doteq 0.02$
	subtotal	87	44	43	
history of eradication, 10 cases	success	6	2	4	$6/10 = 0.6$
	failure	4	3	1	$4/10 = 0.4$
	subtotal	10	5	5	
	Total number	97	49	48	

19. Eradication success rate for drug combination type (initial eradication 87 cases)

Combination types of eradication drugs		success	drug allergy	failure	undecided	total	Rate of success	P value
(1)AMPC + CAM (first-line regime)	PPI use	15	0	1	0	16	0.938	
	VPZ use	18	0	0	1	19	0.947	
	subtotal	33	0	1	1	35	0.943	
(2)AMPC + MNZ (second-line regimen)	PPI use	12	0	1	0	13	0.923	
	VPZ use	10	0	0	1	11	0.909	
	subtotal	22	0	1	1	24	0.917	0.84(1vs2)
(3)Other than above (third-line regimen)	PPI use	13	1	1	0	15	0.867	
	VPZ use	13	0	0	0	13	1.000	
	subtotal	26	1	1	0	28	0.929	0.81(1vs3) 0.79(2vs3)
	total	81	1	3	2	87	0.931	

20. Eradication success rate for drug combination type (10 patients with previous eradication)

Combination types of eradication drugs		success	failure	total	Rate of success	P value
(1)AMPC + CAM (first-line regime)	PPIuse	0	1	1	0	
	VPZuse	0	0	0		
	subtotal	0	1	1	0	0.375(1vs3)
(2)AMPC + MNZ (second-line regimen)	PPIuse	0	1	1	0	
	VPZuse	1	0	1	1	
	subtotal	1	1	2	0.50	0.667(1vs2)
(3)Other than above(third-line regimen)	PPIuse	2	1	3	0.67	
	VPZuse	3	1	4	0.750	
	subtotal	5	2	7	0.714	0.583(2vs3)
	total	6	4	10	0.6	

21.Eradication success rate (Initial eradication ,87 cases) Re-view

	result	number	Percentage
Initial eradication ,87 cases	success	81	93.1%*
	failure	3**	3.4%
	Terminated due to allergy	1	1.1%
	No follow-up	2*	2.3%
	total	87	

***If excluded 2 no follow-up cases, success rate becomes 95.3%.**

**** Two cases have been eradicated by following regimen, but one declined .**

22.Recent reports of success-ratio for Helicobacter pylori eradication

	authority	Theme	Regimen
2	2019.6.WS1-2(the 25th Annual meeting of the Japanese society for Helicobacter Research) Yuji Shimada et al.	Gender and age-specific first-line eradication rate of Helicobacter pylori	Standard regime
3	2019.6.WS1-4 Soichiro Sue et al.	VPZ-based 1st line triple therapy with MNZ(VAM) for CAM resistant HP	
4	2019.6.WS1-5 Takashi Ando et al.	The usefulness of Helicobacter pylori eradication therapy based on CAM susceptibility in PCAB era.	
5	The Journal of the Japanese Society of Clinical Internal Medicine Vol. 32, No. 1 p110-116.2017 Tomoyuki Kuramitsu	Our clinic's approach to H. pylori eradication treatment.	Selected P-CAB group. In case of third-line eradication , STFX was used for 7days
6	2019.6.WS1-6 Tatsuhiko Masaoka et al.	Efficacy and safety of vonoprazan including regimen as a third-line H.pylori eradication therapy	STFX200mg/Day AMPC2000mg/Day VPZ40mg/Day × 7days
7	2019.6.WS1-7 Sayoko Kiwaki et al.	Out comes of third-line Helicobacter pylori eradication with regimens consisting Vonoprazan	AMPC+ STFX + (RPZ or VPZ)

23.Comparison of success rates for first-line eradication

Report number	reporter	Case numbers	Success numbers	Initial eradication success ratio (ITT)	Initial eradication success ratio (PP)	P-value (1 vs each report ITT)
1	Tsuneo araki 2023	87	81	0.931	0.953	-
2	Yuji Shimada et al.2019	596	525	0.881	0.919	0.703
3	Soichiro Sue et al.2019	30	29	0.967	1	0.423
4	Takashi Ando et al.2019	95	94	-	VAC:50/50=1 VAM:43/43=1	0.0614 0.0847(used PP)
5	Tomoyuki Kuramitsu.2017	232	202	0.871	0.902	0.129

24.Eradication success rate (history of eradication,10cases)

Re-view

	result	number	Percentage
History of eradication, 10 cases	success	6*	60%
	failure	4**	40%
	total	10	

* All 6 cases have experienced only one-time past eradication.

**Two cases have experienced two-time past eradication, one case: 3-time, one case :4-time.

**Finally all 4 cases have been eradicated by following one or two regimen.

25. Comparison of success rates for second-line eradication

Report number	reporter	Case numbers	Success numbers	Second eradication success ratio (ITT)	second eradication success ratio (PP)	P-value (1 vs each report ITT)
1	Tsuneo araki 2023	6	6	1	1	-
5	Tomoyuki Kuramitsu 2017	47	42	0.894	1	0.535

26. Comparison of success rates for more than third line eradication

Report number	reporter	Case numbers	Success numbers	More than third eradication success ratio (ITT)	More than third eradication success ratio (PP)	P-value (1 vs each report ITT)
1	Tsuneo araki 2023	4	0	0	0	-
5	Tomoyuki Kuramitsu 2017	7	7 or 6	1 or 0.86	$(7 \text{ or } 6) / (7 \text{ or } 6) \doteq 1 \text{ or } 0.86$	0.003 or 0.0152
6	Tatsuhiro Masaoka et al. 2019	75	68	0.907	$68 / 72 \doteq 0.944$	0.0002
7	Sayoko Kiwaki et al. 2019	69 (RPZ) 115 (VPZ)	44 81	0.638 0.704	$44 / 67 \doteq 0.657$ $81 / 112 \doteq 0.723$	0.0218 0.0093

Our result is clearly inferior than another reports and Significantly deferent.

27. Gastrointestinal Endoscopy Findings 1

Gastrointestinal endoscopic findings in 97 H. pylori culture-positive cases (black and bolded are findings related to H. pylori infection)	Number of cases (with duplicates)	frequency	note
1. chronic gastritis	97	1.00	Biopsy performed in 18 cases (0.19)
2. Edema and redness of gastric mucosa	90	0.93	
3. atrophic gastritis	63	0.65	
3. erosion	37	0.38	
4. slipped hernia of the hilum	36	0.37	
5. Many fine bumps and irregularities	33	0.34	
6. reflux esophagitis	33	0.34	
7. Duodenal ulcer or scar	17	0.18	
8. gastric polyp	13	0.13	Including hyperplastic polyps
9. gastric xanthoma	10	0.10	
10. hyperplastic polyp	9	0.09	
11. chicken skin gastritis	6	0.06	
12. fold enlargement	5	0.05	
13. Gastric ulcer or scar	4	0.04	

28. Gastrointestinal Endoscopy Findings 2

Gastrointestinal endoscopic findings in 97 H. pylori culture-positive cases (black and bolded are findings related to H. pylori infection)	Number of cases (with duplicates)	frequency	note
14. RAC in some areas (regular arrangement of collecting venules)	4	0.04	Suggestive of H. pylori non-infection.
15. Intestinal epithelial metaplasia	4	0.04	
16. Hematin adhesion	3	0.03	pylori non-infection was suggested.
17. telangiectasia	3	0.03	
18. waterfall stomach	2	0.02	(same person)
19. Viscous mucus adhesion	2	0.02	
20.SMT (Gastric submucosal tumor)	2	0.02	
21.Esophageal glycoacanthosis	2	0.02	Hyperplasia of squamous epithelium containing glycogen
22. candidal esophagitis	2	0.02	
23. stomach cancer	1	0.01	Successful preoperative eradication. Pyloric gastrectomy was performed. Postoperative diagnosis stage IA, signet ring cell. No recurrence for 5 years.
24.gastric adenoma	1	0.01	gastric adenoma
25. gastric fundic gland polyp	1	0.01	pylori non-infection was suggested.

29.conclusion

- (1) The success rates of first and second-line eradication of H. pylori using five antimicrobial susceptibility tests were 93%、100%、 respectively, which were no significant differences compared to previous reports.**
- (2) But the success rate of more than third-line eradication using that was obviously inferior compared to previous reports.**
- (3) Nevertheless its test were useful for the following eradication ended success.**
- (4) Thus five antimicrobial susceptibility test is a good guide as the Miotsukushi.**

