Table 4 HR of regression from non-smoking CIN1/2 according to the serum micronutrients and nutrient intake questionnaire

	n	Person-months	Events	Cumulative 2-year rate (95 % CI)	Hazard ratio for regression (95 % CI)			
					Unadjusted	*p* value	Adjusted model	*p* value
Serum retinol							*p* for trend	0.292
Low (<55.2)	62	809.8	39	67.0 (54.5–79.0)	1		1	
Medium (55.2–67.9)	70	922.3	41	62.8 (50.9–74.6)	0.93 (0.60–1.44)	0.75	1.03 (0.65–1.63)	0.908
High (>67.9)	58	743.4	39	71.4 (58.7–83.1)	1.08 (0.69–1.68)	0.742	1.21 (0.74–1.98)	0.448
Serum α-carotene							*p* for trend	0.883
Low (<5.1)	46	560.7	28	64.4 (50.1–78.5)	1.00		1.00	
Medium (5.1–9.7)	62	789.7	38	66.1 (53.3–78.4)	0.97 (0.60–1.59)	0.918	1.22 (0.73–2.05)	0.449
High (>9.7)	82	1,125.1	53	68.7 (57.9–79.0)	0.93 (0.59–1.47)	0.76	1.26 (0.75–2.11)	0.384
Serum β-carotene							*p* for trend	0.206
Low (<28.3)	45	583.9	26	60.1 (45.8–74.7)	1.00		1.00	
Medium (28.3–57.6)	61	780.1	41	75.7 (62.7–86.9)	1.16 (0.71–1.90)	0.557	1.20 (0.71–2.03)	0.488
High (>57.6)	84	1,111.5	52	65.5 (54.8–76.0)	1.03 (0.64–1.65)	0.91	1.23 (0.73–2.07)	0.439
Serum zeaxanthin/lutein							*p* for trend	0.024
Low (<42.9)	56	729.3	34	64.8 (51.4–77.8)	1.00		1.00	
Medium (42.9–57.3)	61	817.3	38	66.7 (54.2–78.9)	1.00 (0.63–1.59)	1	1.12 (0.69–1.84)	0.642
High (>57.3)	73	928.9	47	68.6 (57.1–79.5)	1.05 (0.68–1.64)	0.813	1.25 (0.78–2.01)	0.352
Serum cryptoxanthin							*p* for trend	0.129
Low (<11.2)	47	650.1	28	64.7 (50.0–79.1)	1.00		1.00	
Medium (11.2–22.1)	61	740.7	38	68.2 (55.3–80.4)	1.23 (0.75–2.00)	0.414	1.24 (0.74–2.08)	0.412
High (>22.1)	82	1,084.7	53	67.5 (56.8–77.8)	1.16 (0.73–1.83)	0.536	1.35 (0.82–2.22)	0.231
Serum lycopene							*p* for trend	0.269
Low (<19.8)	63	805.3	37	63.2 (50.7–75.7)	1.00		1.00	
Medium (19.8–35.8)	63	827.7	43	73.8 (61.5–84.8)	1.11 (0.71–1.72)	0.651	1.17 (0.73–1.87)	0.51
High (>35.8)	64	842.5	39	64.3 (52.0–76.4)	1.00 (0.63–1.55)	0.962	1.28 (0.79–2.07)	0.316
Serum α-tocopherol							*p* for trend	0.176
Low (<753.0)	60	731.7	39	67.1 (54.7–79.0)	1.00		1.00	
Medium (753.0–983.9)	63	829.9	40	67.5 (55.2–79.2)	0.91 (0.59–1.42)	0.676	0.96 (0.60–1.53)	0.866
High (>983.9)	67	913.9	40	66.5 (53.9–78.6)	0.81 (0.52–1.26)	0.344	0.96 (0.60–1.54)	0.859
Retinol intake							*p* for trend	0.892
Low (<190.2)	62	760.7	36	63.5 (50.5–76.4)	1.00		1.00	
Medium (190.2–313.1)	63	840.7	41	70.4 (57.9–82.0)	1.04 (0.67–1.63)	0.854	0.90 (0.53–1.54)	0.704
High (>313.1)	65	874.1	42	66.3 (54.5–77.7)	1.02 (0.65–1.59)	0.94	0.86 (0.48–1.53)	0.61
Carotene intake							*p* for trend	0.131
Low (<3,281.4)	47	606.4	29	67.7 (52.7–81.9)	1.00		1.00	
Medium (3,281.4–5,042.8)	71	959.6	40	62.1 (50.0–74.2)	0.88 (0.55–1.43)	0.615	0.89 (0.51–1.56)	0.676
High (>5,042.8)	72	909.5	50	70.8 (59.8–81.0)	1.16 (0.74–1.84)	0.515	1.08 (0.60–1.94)	0.804
Vitamin A intake							*p* for trend	0.134
Low (<2,398.8)	50	676.0	28	63.5 (48.8–78.2)	1.00		1.00	
Medium (2,398.8–3,466.7)	69	934.1	41	63.8 (51.7–75.8)	1.08 (0.67–1.75)	0.755	1.14 (0.65–1.99)	0.654
High (>3,466.7)	71	865.4	50	72.3 (61.3–82.4)	1.42 (0.89–2.25)	0.14	1.47 (0.79–2.73)	0.218
Vitamin E intake							*p* for trend	0.163
Low (<6.7)	51	631.5	29	61.3 (47.4–75.5)	1.00		1.00	
Medium (6.7–8.7)	62	884.3	39	66.0 (53.6–78.1)	0.98 (0.61–1.58)	0.932	1.38 (0.70–2.71)	0.354
High (>8.7)	77	959.7	51	70.3 (59.3–80.6)	1.16 (0.74–1.83)	0.519	1.44 (0.67–3.12)	0.352

Cox's proportional hazard model showing the hazard ratio for regression in a cumulative 24-month period in non-smokers. The adjusted model was identical to the model used in Table 3. The units of micronutrients are expressed as μg/dL

Table 5 HR of regression from current smoking CIN1/2 according to the serum micronutrients and nutrient intake questionnaire

	n	Person-months	Events	Cumulative 2-year rate (95 % CI)	Hazard ratio for regression (95 % CI)			
					Unadjusted	*p* value	Adjusted model	*p* value
Serum retinol							*p* for trend	0.43
Low (<55.2)	47	614.0	27	64.0 (49.2–78.6)	1		1	
Medium (55.2–67.9)	38	417.6	24	70.5 (53.4–85.7)	1.29 (0.74–2.23)	0.369	1.54 (0.87–2.76)	0.141
High (>67.9)	57	780.5	21	42.9 (30.1–58.3)	0.60 (0.34–1.06)	0.08	0.54 (0.29–1.00)	0.05
Serum α-carotene							*p* for trend	0.898
Low (<5.1)	59	751.9	33	62.5 (49.2–75.8)	1.00		1.00	
Medium (5.1–9.7)	53	689.6	22	49.9 (35.3–66.7)	0.72 (0.42–1.24)	0.24	0.85 (0.48–1.53)	0.595
High (>9.7)	30	370.6	17	61.8 (43.6–80.2)	1.04 (0.58–1.87)	0.886	1.23 (0.63–2.39)	0.537
Serum β-carotene							*p* for trend	0.667
Low (<28.3)	63	788.0	31	58.1 (44.6–72.2)	1.00		1.00	
Medium (28.3–57.6)	53	700.2	27	54.5 (41.1–69.1)	1.02 (0.61–1.71)	0.94	1.07 (0.62–1.86)	0.808
High (>57.6)	26	323.9	14	66.6 (44.5–87.0)	1.06 (0.56–2.00)	0.854	1.04 (0.51–2.14)	0.915
Serum zeaxanthin/lutein							*p* for trend	0.373
Low (<42.9)	54	640.8	32	63.6 (50.0–77.0)	1.00		1.00	
Medium (42.9–57.3)	52	669.4	26	54.1 (40.4–69.0)	0.79 (0.47–1.33)	0.372	0.88 (0.51–1.52)	0.645
High (>57.3)	36	501.9	14	57.6 (37.9–78.8)	0.55 (0.29–1.02)	0.059	0.76 (0.37–1.53)	0.435
Serum cryptoxanthin							*p* for trend	0.866
Low (<11.2)	62	727.3	36	67.4 (53.9–80.2)	1.00		1.00	
Medium (11.2–22.1)	47	644.3	20	48.4 (33.9–65.2)	0.63 (0.36–1.09)	0.098	0.72 (0.39–1.31)	0.279
High (>22.1)	33	440.5	16	53.9 (36.6–73.1)	0.73 (0.40–1.31)	0.286	0.85 (0.44–1.64)	0.63
Serum lycopene							*p* for trend	0.517
Low (<19.8)	43	543.8	21	55.3 (39.9–71.9)	1.00		1.00	
Medium (19.8–35.8)	55	761.7	29	60.8 (46.7–75.1)	0.96 (0.55–1.69)	0.896	0.79 (0.42–1.48)	0.457
High (>35.8)	44	506.6	22	54.4 (39.2–70.9)	1.08 (0.59–1.96)	0.802	0.77 (0.38–1.54)	0.456
Serum α-tocopherol							*p* for trend	0.042
Low (<753.0)	53	594.2	34	68.8 (55.5–81.4)	1.00		1.00	
Medium (753.0–983.9)	49	718.2	19	43.5 (30.1–59.7)	0.47 (0.27–0.83)	0.009	0.53 (0.27–0.94)	0.03
High (>983.9)	40	499.7	19	66.7 (46.0–86.0)	0.64 (0.36–1.11)	0.114	0.76 (0.42–1.40)	0.383
Retinol intake							*p* for trend	0.58
Low (<190.2)	50	573.8	29	62.3 (48.3–76.4)	1.00		1.00	
Medium (190.2–313.1)	51	673.9	25	56.5 (42.1–71.9)	0.74 (0.43–1.26)	0.263	0.76 (0.42–1.37)	0.36
High (>313.1)	41	564.4	18	52.3 (36.2–70.6)	0.63 (0.35–1.13)	0.124	0.57 (0.29–1.13)	0.106
Carotene intake							*p* for trend	0.182
Low (<3,281.4)	64	730.7	34	59.8 (46.9–73.1)	1.00		1.00	
Medium (3,281.4–5,042.8)	43	632.0	22	58.7 (42.7–75.4)	0.72 (0.42–1.24)	0.238	0.71 (0.39–1.31)	0.272
High (>5,042.8)	35	449.4	16	52.9 (35.8–72.2)	0.73 (0.41–1.33)	0.309	0.55 (0.25–1.18)	0.122
Vitamin A intake							*p* for trend	0.268
Low (<2,398.8)	65	723.6	36	61.9 (49.1–74.9)	1.00		1.00	
Medium (2,398.8–3,466.7)	43	642.5	19	49.1 (34.4–66.2)	0.59 (0.34–1.03)	0.064	0.58 (0.31–1.07)	0.081
High (>3,466.7)	34	446.0	17	60.6 (42.2–79.4)	0.74 (0.42–1.32)	0.307	0.60 (0.28–1.32)	0.208
Vitamin E intake							*p* for trend	0.567
Low (<6.7)	61	684.0	32	56.7 (44.1–70.1)	1.00		1.00	
Medium (6.7–8.7)	45	720.6	19	49.0 (34.4–66.0)	0.56 (0.32–0.99)	0.047	0.51 (0.25–1.05)	0.066
High (>8.7)	36	407.5	21	67.3 (49.6–83.8)	1.02 (0.59–1.77)	0.947	0.56 (0.23–1.38)	0.211

Cox's proportional hazard model showing the hazard ratio for regression in a cumulative 24-month period in current smokers only. The adjusted model was identical to the model used in Table 3. The units of micronutrients are expressed as μg/dL

Table 6 HR of progression from entire CIN1/2 according to the serum micronutrients and nutrient intake questionnaire

	n	Person-months	Events	Cumulative 5-year rate (95 % CI)	Hazard ratio for progression (95 % CI)			
					Unadjusted	*p* value	Adjusted model	*p* value
Serum retinol							*p* for trend	0.372
Low (<55.2)	128	4,588.2	7	8.7 (3.6–20.1)	1.00		1.00	
Medium (55.2–67.9)	132	5,048.8	17	17.1 (10.8–26.6)	2.25 (0.93–5.44)	0.071	2.35 (0.95–5.77)	0.063
High (>67.9)	131	5,210.1	14	14.3 (8.5–23.7)	1.82 (0.73–4.51)	0.198	2.23 (0.88–5.60)	0.089
Serum α-carotene							*p* for trend	0.669
Low (<5.1)	127	4,506.6	13	15.4 (8.7–26.2)	1.00		1.00	
Medium (5.1–9.7)	133	4,955.5	17	16.0 (10.0–25.0)	1.21 (0.59–2.49)	0.609	1.08 (0.51–2.31)	0.835
High (>9.7)	131	5,385.0	8	9.6 (4.7–19.0)	0.52 (0.22–1.27)	0.153	0.46 (0.18–1.15)	0.098
Serum β-carotene							*p* for trend	0.337
Low (<28.3)	129	4,245.0	18	21.8 (13.6–33.9)	1.00		1.00	
Medium (28.3–57.6)	131	5,208.1	7	7.0 (3.2–14.7)	0.32 (0.13–0.77)	0.011	0.28 (0.11–0.71)	0.007
High (>57.6)	131	5,394.0	13	13.2 (7.7–22.3)	0.58 (0.28–1.19)	0.14	0.52 (0.24–1.13)	0.098
Serum zeaxanthin/lutein							*p* for trend	0.772
Low (<42.9)	130	4,611.4	11	12.1 (6.7–21.4)	1.00		1.00	
Medium (42.9–57.3)	130	5,291.5	17	17.9 (11.2–28.0)	1.37 (0.64–2.94)	0.415	1.58 (0.71–3.53)	0.266
High (>57.3)	131	4,944.2	10	9.4 (5.1–17.1)	0.87 (0.37–2.06)	0.756	0.95 (0.39–2.32)	0.908
Serum cryptoxanthin							*p* for trend	0.618
Low (<11.2)	129	4,591.6	12	12.2 (6.9–20.9)	1.00		1.00	
Medium (11.2–22.1)	130	4,906.2	16	17.1 (10.6–27.0)	1.26 (0.60–2.67)	0.544	1.37 (0.61–3.06)	0.445
High (>22.1)	132	5,349.3	10	10.5 (5.5–19.7)	0.73 (0.32–1.69)	0.465	0.71 (0.29–1.72)	0.450
Serum lycopene							*p* for trend	0.286
Low (<19.8)	129	4,827.0	15	17.5 (10.5–28.3)	1.00		1.00	
Medium (19.8–35.8)	131	4,954.6	11	10.0 (5.6–17.6)	0.71 (0.33–1.55)	0.395	0.61 (0.27–1.36)	0.223
High (>35.8)	131	5,065.5	12	13.1 (7.3–22.9)	0.76 (0.36–1.63)	0.48	0.73 (0.33–1.59)	0.428
Serum α-tocopherol							*p* for trend	0.788
Low (<753.0)	128	5,143.1	11	12.0 (6.6–21.2)	1.00		1.00	
Medium (753.0–983.9)	132	5,052.6	11	13.3 (7.4–23.3)	1.01 (0.44–2.33)	0.983	0.91 (0.39–2.10)	0.820
High (>983.9)	131	4,651.4	16	15.7 (9.3–25.8)	1.60 (0.74–3.45)	0.232	1.87 (0.84–4.19)	0.126
Retinol intake							*p* for trend	0.666
Low (<190.2)	130	4,778.5	14	14.7 (8.6–24.4)	1.00		1.00	
Medium (190.2–313.1)	130	4,985.2	15	16.7 (9.8–27.7)	1.02 (0.49–2.12)	0.948	1.08 (0.51–2.32)	0.834
High (>313.1)	131	5,083.4	9	9.5 (4.9–17.7)	0.60 (0.26–1.40)	0.239	0.62 (0.23–1.68)	0.346
Carotene intake							*p* for trend	0.331
Low (<3,281.4)	130	4,578.9	9	10.8 (5.2–21.6)	1.00		1.00	
Medium (3,281.4–5,042.8)	131	4,789.0	16	17.6 (11.4–26.7)	2.02 (0.91–4.46)	0.083	2.30 (0.97–5.42)	0.058
High (>5,042.8)	130	5,479.2	10	11.6 (6.2–21.0)	0.94 (0.38–2.33)	0.901	1.19 (0.41–3.44)	0.746
Vitamin A intake							*p* for trend	0.493
Low (<2,398.8)	130	4,510.5	11	12.2 (6.3–22.9)	1.00		1.00	
Medium (2,398.8–3,466.7)	131	4,921.0	16	15.1 (9.4–23.9)	1.33 (0.62–2.87)	0.463	1.32 (0.59–2.97)	0.500
High (>3,466.7)	130	5,415.6	11	12.6 (3.8–22.2)	0.84 (0.36–1.95)	0.689	0.92 (0.33–2.54)	0.873
Vitamin E intake							*p* for trend	0.834
Low (<6.7)	130	4,431.0	12	13.8 (7.5–24.7)	1.00		1.00	
Medium (6.7–8.7)	130	5,128.1	15	14.1 (8.6–22.6)	1.08 (0.51–2.31)	0.842	1.06 (0.44–2.56)	0.892
High (>8.7)	131	5,288.0	11	12.5 (6.8–22.1)	0.78 (0.34–1.77)	0.55	1.00 (0.30–3.38)	0.998

Cox's proportional hazard model showing the hazard ratio for progression over a cumulative 60-month period. The adjusted model was identical to the model used in Table 3. The units of micronutrients are expressed as μg/dL

effects were weaker or not found with a higher level of serum beta-carotene (HR 0.52, 95 % CI 0.24–1.13, $p = 0.098$). In contrast, a high carotene intake did not show an inverse relationship, but rather a non-significant increase in progression (HR 2.30, 95 % CI 0.97–5.42, $p = 0.058$). There was no significant association between other serum micronutrients and risk for CIN progression.

Discussion

The role of environmental factors, including micronutrients and tobacco smoking, in cervical carcinogenesis has been discussed. Smoking status in particular interfered with serum levels and intake of carotenoids as shown in Tables 1 and 2. In smokers, food intake is intrinsically lower than in non-smokers [22]. From the questionnaires, the intake per day of all micronutrients, except retinol and tocopherol, was lower in current smokers than in non-smokers, suggesting an unbalanced diet resulting from either smoking or other lifestyle behaviors (Table 1). Serum levels of alpha-carotene, beta-carotene and cryptoxanthin were inversely correlated with smoking status, but alpha-tocopherol was not correlated with smoking status after adjusting for age, BMI and frequency of alcohol intake (Table 2). These data were consistent with a previous report in which smoking was shown to affect serum beta-carotene levels but to have no effect on alpha-tocopherol levels [23]. Though alpha-tocopherol and beta-carotene are well known as antioxidants, the antioxidant effect of alpha-tocopherol is not due to a reaction with oxygen. In contrast, beta-carotene does react with oxygen. This suggests that there is a difference in the mechanisms of antioxidant reaction [24].

In regression subjects, we expected to find a protective effect from high serum levels or intake of carotenoids; however, neither of these had protective effects. We assume that smoking status modulates dietary intake or serum levels of micronutrients. Therefore, we investigated the association between dietary intake or serum levels of micronutrients and CIN regression, taking into account smoking status (Tables 3, 4, 5). In non-smoking regression subjects, regression was significantly related to the serum levels of zeaxanthin/lutein. This relationship was not found in current smokers. In a similar example, an isoflavone has a protective effect for lung cancer, but the effect is abolished by smoking [25]. It was reported that zeaxanthin/lutein may be a useful marker of intake of leafy vegetables, spinach, green peas, broccoli and seaweed [26]. Zeaxanthin/lutein is chemically more hydrophilic than other carotenoids such as alpha- and beta-carotene, lycopene and beta-cryptoxanthin. The mechanisms of a potential protection against carcinogenesis may include: induction of apoptosis, inhibition of angiogenesis, enhancement of gap junction intercellular communication, induction of cell differentiation, prevention of oxidative damage, and modulation of the immune system. Serum levels of lutein have been inversely associated with cytochrome CYP1A2 activity, a hepatic enzyme responsible for the metabolic activity of a number of putative human carcinogens [27]. High serum levels of alpha-tocopherol tend to have an inhibitory effect on regression in smokers (Table 4). There is a similar effect in that supplemental vitamin E, presumably causing a high concentration of alpha-tocopherol, is associated with an increased risk of lung cancer, which was confined to current smokers [28]. Alpha-tocopherol is considered to be an antioxidant, but it might act as a pro-oxidant [24].

Though a weak and non-significant protective effect of dietary intake or low serum concentration of beta-carotene has been observed previously [10, 15, 29, 30], we found that a medium serum level of beta-carotene showed a significant protective effect on CIN progression, whereas this protective effect at higher serum levels of beta-carotene was weaker or abolished (Table 6). These data appear to be consistent with in-vitro experiments reporting that very high concentrations of beta-carotene decreased antioxidant and/or induced pro-oxidant effects [31, 32]. Based on epidemiological studies that have shown an association between a low intake of carotenes and human cancers [33], an intervention study was conducted for the prevention of lung cancer [34]. However, it was paradoxically reported that high serum levels of beta-carotene induced by oral supplements promoted lung cancer in male heavy smokers aged 50–69 years. In CIN, oral beta-carotene supplementation did not enhance CIN regression in a randomized, double-blind phase III trial [35]. One explanation for these failures may be that oral supplements induced extremely high serum levels of beta-carotene. Taken together, these data suggest that medium serum levels of beta-carotene may interfere with CIN progression or cancer development.

There was a discrepancy between the results of dietary intake and serum levels of beta-carotene. Endogenous metabolic processes may influence the serum concentrations of micronutrients. In fact, inconsistent results of the serum levels and dietary intake of alpha-tocopherol in patients with prostate cancer, and contradictory results of retinol in patients with cervical cancer, have been reported previously [14, 36, 37]. Additionally, there is limited dietary intake information obtained from questionnaires because of inherent recall bias. We examined the residual confounding factors, including passive smoking, the number of sexual partners, and serum *Chlamydia* IgG antibody, in addition to the adjusted model. Despite confounding by other risk factors included for adjustments, the analyses did not change the conclusion.

To our knowledge, this is the first large-scale prospective cohort study for CIN outcome to report an association between serum levels of antioxidant micronutrients adjusted for potential confounders including CIN grade, HPV genotype, age, total energy intake and smoking. To make our comparisons, we investigated not only serum levels but also dietary intake of micronutrients, despite the fact that food-intake questionnaires contain limited information. It is known that the accuracy of recalling past dietary intake is influenced by current dietary habits [38]. There are inconsistent results between previous case–control and cohort studies. However, our discrepant results did not reach the conclusion that women with CIN received a benefit from consuming a beta-carotene-rich diet. However, not smoking and maintaining high serum levels of zeaxanthin/lutein, presumably by intake of leafy vegetables, spinach, green peas, broccoli, and seaweed, are advantageous for the prevention of cervical cancer.

This study has some potential limitations. We included only CIN patients with an available serum sample for measurement of serum nutrients [18]. The majority of CIN patients already had persistent HPV infection at enrollment in the present study. If these nutrients play an important role in preventing persistent HPV infection, we cannot determine that role in this cohort study. The food intake contains not only the micronutrients being investigated but also other nutrients and mixtures. The incident number of progression cases was small and it was difficult to analyze by smoking status. A large-scale cohort study with a longer period of observation is required to clarify the association between serum levels or dietary intake of micronutrients and the risk of developing cervical cancer.

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Conflict of interest The authors declare that they have no conflict of interest.

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Clinical efficacy of sitafloxacin 100 mg twice daily for 7 days for patients with non-gonococcal urethritis

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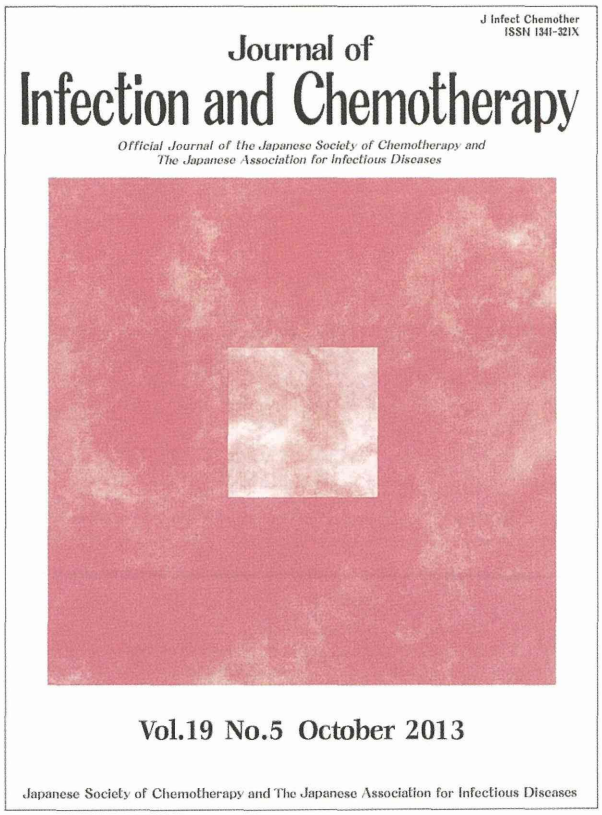

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ORIGINAL ARTICLE

Clinical efficacy of sitafloxacin 100 mg twice daily for 7 days for patients with non-gonococcal urethritis

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Abstract To clarify the clinical efficacy of STFX for patients with non-gonococcal urethritis (NGU), including chlamydial urethritis and *Mycoplasma genitalium*-positive urethritis, this study included male patients with NGU who were 20 years old or older. The pathogens, including *Chlamydia trachomatis*, *M. genitalium* and *Ureaplasma urealyticum*, were detected by nucleic acid amplification tests and the patients were treated with sitafloxacin 100 mg twice daily for 7 days. Microbiological and clinical efficacies were assessed for the patients with NGU posttreatment. Among the 208 patients enrolled in this study, data for a total of 118 patients could be analyzed. The median age was 32 (20–61) years. The median duration from the completion of treatment to the second visit was 21 (14–42) days. There were 68 pathogen-positive NGU cases and 50 with NGU without any microbial detection. Microbiological cure was achieved in 95.6 % of the pathogen-positive NGU patients. Total clinical cure was achieved in 91.3 % (105/115). In this study, STFX was able to eradicate 95.7 % of *C. trachomatis*, 93.8 % of *M. genitalium* and 100 % of *U. urealyticum*. The results of our clinical research indicate that the STFX treatment regimen should become a standard regimen recommended for patients with NGU. In addition, this regimen is recommended for patients with *M. genitalium*-positive NGU.

Keywords Urethritis · *Chlamydia trachomatis* · *Mycoplasma genitalium* · *Ureaplasma urealyticum* · Sitafloxacin

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Introduction

The principal pathogen of male non-gonococcal urethritis (NGU) is *Chlamydia trachomatis* [1–3]. To date, a few antimicrobial agents for the treatment of chlamydial urethritis have been highly effective [2–4] and are recommended as standard treatment regimens [5]. *Mycoplasma genitalium* is also a pathogen of male NGU [6] and its frequency as an isolated pathogen from NGU is generally second to that of *C. trachomatis* [2, 3]. Although azithromycin (AZM) 1 g stat, one of the recommended treatment regimens for patients with chlamydial urethritis, has maintained its efficacy for almost all patients with *M. genitalium*-positive NGU, recent reports show that there are some cases with AZM treatment failure due to AZM-resistant strains [7]. When patients with NGU are treated, the ideal treatment regimen must be effective for both *C. trachomatis* and *M. genitalium*. Unfortunately, gatifloxacin (GFLX) [8], which appeared to be an ideal antimicrobial agent, is no longer available because of adverse events, which led to its withdrawal.

Sitafloxacin (STFX) is a new-generation fluoroquinolone and highly active against *C. trachomatis* [9] and *M. genitalium* [10]. Its antimicrobial activity is unique compared to those of conventional fluoroquinolones [11]. Although STFX is expected to have potential efficacy for patients with NGU, few clinical studies have so far been done, though there is one Japanese study [12]. The aim of this study was to clarify the clinical efficacy of STFX for patients with NGU, including chlamydial urethritis and *M. genitalium*-positive urethritis.

Materials and methods

Study design

This prospective, single-arm, open-label, clinical study was done during the period from October 2010 to September 2012.

Patients

This study included heterosexual male patients with NGU who were 20 years old or older. Diagnosis was determined by certified urologists according to the Japanese guidelines for clinical research [13]. They conducted interviews about the symptoms and adverse events and then prescribed the drug. Symptomatic and asymptomatic patients were defined as described in a previous report [3]. In short, symptomatic patients were defined as having urinary tract symptoms including pain on voiding, pus discharge and so on. Asymptomatic patients with NGU were included if only *C. trachomatis* was detected. These asymptomatic patients commonly visited the clinic because their female sexual partners were diagnosed as having a genital chlamydial infection. Patients were excluded from this study if they had a history of allergy to STFX, renal dysfunction, a history of epilepsy, were infected with *Neisseria gonorrhoeae* or needed other antimicrobial agents. As the treatment, all patients received a 100 mg tablet twice daily for 7 days orally.

Procedures for detection of pathogens

At the clinic, about 20 ml of the first-voided urine (FVU) was taken from each patient and used as a specimen. *C. trachomatis* and *N. gonorrhoeae* were detected with the APTIMA COMBO 2 transcription-mediated amplification assay (Gen-Probe, Inc., San Diego, CA, USA) using 2 ml of the FVU specimen. Then 8 ml of the FVU specimen were stored in a freezer at the laboratory of the Department of Urology, University of Occupational and Environmental Health, Japan, for subsequent detection of *M. genitalium* and *Ureaplasma urealyticum*. Of the 8 ml urine specimen, 1.9 ml was centrifuged at 10 000 *g* for 15 min and the pellet was mixed with 20 % Chelx 100 (Bio-Rad Laboratories, Hercules, CA, USA). This mixture was heated at 95 °C for 10 min and used as a template for the nucleic acid amplification test [14, 15].

M. genitalium was detected by real-time PCR as described by Jensen [15–17] and specimens that had more than 10 genome equivalents (geq) were determined to be positive for *M. genitalium*. The positive specimens were reexamined by 16S rRNA PCR for confirmation [18]. Isolation of *M. genitalium* was attempted using the urine sediment from positive urine specimens as described previously [17].

U. urealyticum was also detected by real-time PCR (TaqMan assay). The primer for *U. urealyticum* was set on a fragment of the *UreaA* gene. The forward primer used was urea-195F 5′-GCAAGAAGACGTTTAGCTAGAGG TTT-3′. The reverse primer was urea8-r 5′-CACGAGCA-GATTGCATTAAGTCAG-3′. The probe was urea8 taqman 5′-FAM-TAATTACTGACCACGTAGTGGA-MGB-3′ for *U. urealyticum*. The sequence of the internal process control (IPC) probe used was 5′-TAMRA-TCCTTCGTGATATC GGACGTTGGCTG-BHQ2-3′. The IPC was constructed as in Jensen's method and the same primers and IPC probe as for *M. genitalium* were used. The Taqman assay for *U. urealyticum* was performed using the same conditions as for *M. genitalium* [15]. The specimens that had more than 10 geq of *U. urealyticum* were determined to be positive.

Microbiological outcome

According to the Japanese guidelines for clinical research [13], the primary outcome of whether pathogens, including

C. trachomatis, *M. genitalium* and *U. urealyticum*, are eradicated is determined 2–4 weeks after the completion of treatment [13]. In this study, if patients had no sexual intercourse until the second visit, we accepted the data of patients who revisited at a maximum 6 weeks after the completion of treatment. As the microbiological outcome, microbiological eradication was defined as the pathogen not being detected by posttreatment nucleic acid amplification tests, and failure was defined as the pathogen still being detected by posttreatment nucleic acid amplification tests [13].

Clinical outcome

In the patients with both pathogen-positive NGU and NGU without any microbial detection, the clinical outcome of whether the symptoms derived from urethritis disappeared was determined 2–4 weeks after the completion of treatment. Asymptomatic *C. trachomatis*-positive and *M. genitalium*-positive patients were excluded from the evaluation of the clinical outcome. As the clinical outcome, cure was defined as no posttreatment symptoms beng observed and failure was defined as posttreatment symptoms derived from urethritis continuing and/or a change of the treatment regimen being necessary due to an unfavorable clinical course [13].

Assessment of adverse events

At the second visit, all patients were interviewed as to whether adverse events, including abdominal pain, diarrhea, nausea and so on, occurred or not.

Ethical considerations

The details of this research project were approved the Review Board in Sapporo Medical University Hospital (http://web.sapmed.ac.jp/byoin/chiken/irb.html; Nos. 22–59, 23–1193, 23–3057) and written informed consent was obtained from each subject. This study was registered in the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR; http://www.umin.ac.jp/ctr/index-j.htm; UMIN ID: UMIN000004509).

Results

A total of 208 patients who were diagnosed as having NGU were enrolled in this study; however, 90 patients were excluded from further analysis. These 90 patients were divided into 18 patients who were diagnosed with gonococcal urethritis by TMA assay, 36 who failed to visit again and were lost, 34 patients whose second visits were too early to evaluate the outcome, one patient who had sexual intercourse with his girlfriend before the second visit and one patient whose data were lost. Finally, data for a total of 118 patients with NGU could be analyzed.

The median age of these patients was 32 years (range: 20–61). The median duration from the completion of treatment to the second visit was 21 (14–42) days. There were 68 cases that were positive for the tested microorganisms and 50 without any microbial detection. In pathogen-positive NGU cases, *C. trachomatis*, *M. genitalium* and *U. urealyticum* were detected from 47, 16 and 17 patients, respectively (Table 1). Of the patients with chlamydial NGU, two were diagnosed as having asymptomatic NGU. In the patients with *M. genitalium*-positive NGU, one was asymptomatic. These three patients were excluded from the analysis of the clinical outcome.

Microbiological cure was achieved in 95.6 % of pathogen-positive NGU. The microbiological eradication rates were 95.7 % (45/47), 93.8 % (15/16) and 100 % (17/17) for *C. trachomatis*, *M. genitalium* and *U. urealyticum*, respectively. The two patients with treatment failure for *C. trachomatis*-positive NGU obtained a clinical cure; but the first one was positive for *C. trachomatis* both 14 and 21 days after the completion of drug administration. The second one was positive for *C. trachomatis* 30 days after completion. Those two patients could not undergo additional examinations because they were lost to follow-up. There was one patient with treatment failure for *M. genitalium*-positive NGU who was positive for *M. genitalium* 25 days after the completion of treatment with continuous pyuria and could not undergo further examination because he was lost to follow-up.

Total clinical cure was achieved in 91.3 % (105/115) of the cases. The clinical cure rate for the patients with NGU without any microbial detection was 90.0 % (45/50).

Table 1 Results for microbiological and clinical cures in the patients with NGU

Detected pathogen	Number	Microbiological cure (%)	Clinical cure (%)
C. trachomatis	36	35/36 (97.2 %)	30/34 (88.2 %)
C. trachomatis *M. genitalium*	4	4/4 (100)	4/4 (100)
C. trachomatis *U. urealyticum*	7	6/7 (85.7)	6/7 (85.7)
M. genitalium	11	10/11 (90.9)	10/10 (100)
U. urealyticum	9	9/9 (100)	9/9 (100)
M. genitalium *U. urealyticum*	1	1/1 (100)	1/1 (100)
Total	68	65/68 (95.6)	60/65 (92.3)

In assessment of adverse events, two patients (1.7 %) had mild diarrhea. However, their symptoms were self-limited and disappeared without further medication.

Discussion

The most important current issue in the treatment strategy for patients with NGU has been the management for *M. genitalium*. *C. trachomatis* is the principal pathogen in NGU and treatment efficacy against chlamydial urethritis is high with standard treatment regimens [5, 19]. In Japan, the current standard treatment regimens are still effective for patients with chlamydial urethritis [2, 3]. However, there have been some reports that the standard treatment regimens are not good enough for patients with *M. genitalium*-positive NGU [7, 20]. In addition, surprisingly, a recent report showed that the clinical and microbiological cure rates for patients with NGU were not so high and that treatment failure against *M. genitalium*-positive NGU was common [21, 22]. Therefore, a new treatment regimen for NGU should be developed and applied.

GFLX was one of the new generation fluoroquinolones that had strong activity against both *C. trachomatis* and *M. genitalium* [23]. In addition, an open clinical trial in Japan clearly showed that the clinical efficacy of GFLX against NGU was high [8]. In the study, the microbiological cure rates for *C. trachomatis* and *M. genitalium* were 100 and 83 %, respectively. However, GFLX, which was expected to be an useful against NGU, was withdrawn from the FDA list and is no longer available. STFX is also one of the new generation of fluoroquinolones whose activity is better than for the other fluoroquinolones [24] and is active against *C. trachomatis* [9] and *M. genitalium* [10]. Indeed, STFX was expected to have potential efficacy for patients with NGU, because the susceptibility of *M. genitalium* to STFX was higher than to other antimicrobial agents in an in vitro study [10]. In a recent study from Japan [12], the microbiological eradications rates of *C. trachomatis*, *M. genitalium* and *U. urealyticum* were 100 % (33 of 33), 100 % (11 of 11) and 80 % (8 of 10), respectively. In our study, the microbiological eradication rates of *C. trachomatis*, *M. genitalium* and *U. urealyticum* were 95.7, 93.8 and 100 %, respectively. These results in clinical studies clearly showed that the treatment regimen using STFX had high treatment efficacy against NGU and should become a standard treatment regimen for NGU. In Norway and France, the microbiological and clinical efficacies of moxifloxacin (MFLX) were reported. In a microbiological study from Bordeaux, France [25], MFLX was shown to be highly active against urogenital *M. genitalium* and *C. trachomatis*. In a clinical study from Norway [26], all 27 patients who were positive for *M. genitalium* finally tested negative after the completion of treatment with MFLX 400 mg once daily for 7 days. MFLX is also one of the new generation of fluoroquinolones, similar to STFX, and has higher treatment efficacy than the conventional ones. Unfortunately, however, we cannot prescribe MFLX for patients with NGU, because it is only permitted for patients with respiratory infections in Japan. STFX has activity against *M. genitalium* that is as strong as MFLX in the antimicrobial susceptibility test. Therefore, the results of our study are reasonable.

As supplementary information, if the patients who visited clinic 1–2 weeks after completion of treatment had been included in analysis, the microbiological eradication rates of *C. trachomatis*, *M. genitalium* and *U. urealyticum* would have been 96.7 % (58 of 60), 94.7 % (18 of 19) and 100 % (17 of 17), respectively. These results clearly demonstrate that STFX has high efficacy for treatment of NGU.

In our study, there were few adverse events due to drug action. The main one was mild diarrhea and no one had a serious clinical course. Interestingly, a study including patients with community-acquired pneumonia (CAP) reported that the frequency of adverse STFX reactions was higher than that in our study, and diarrhea occurred in 14.6 % of the patients taking STFX 100 mg sid for 7 days and in 4.17 % of those with STFX 50 mg bid for 7 days [27]. There was no severe event in that study. In the study with CAP, 63.9 % of the patients were 60 years old or older. In our study, the median age of the patients was 32 years. These findings suggest that adverse STFX events, especially diarrhea, occur more frequently in older patients. Although there have been a limited number of studies about STFX, the treatment regimen with STFX can be safely undergone by patients with NGU who are relatively young.

This study has some limitations. The total number of patients included in this study was relatively small. However, the frequency of *M. genitalium* isolation is usually about 7–10 % in NGU in Japan [2, 3, 12]. In a recent study, it was 14.8 % [21] as determined using the same procedures for detection of the organism. The frequency of isolation of *M. genitalium* is relatively so small that it is difficult to study a large number of cases with it in this kind of clinical research. Another limitation is the study design. When the clinical efficacy of antimicrobial agents for urethritis is evaluated, a double-blind, randomized controlled study is ideal to determine the efficacy. However, while AZM 1 g, one of the recommended treatment regimens, can be used for 1-day treatment, the duration of fluoroquinolone treatment is generally a 7-day treatment regimen. Therefore, an exact, strict study design for comparison with AZM is difficult. However, we have various clinical data for NGU and can compare out results with those of our previous reports [2, 3].

In conclusion, our clinical research revealed that the STFX treatment regimen should become the standard one and be recommended for patients with NGU. In addition, this regimen is recommended for patients with *M. genitalium*-positive NGU.

Conflict of interest Tetsuro Matsumoto is a consultant to Daiichi-Sankyo.

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咽頭疾患の診療の進め方

STIとしての咽頭病変

★1
性感染症は従来よりSTD（sexually transmitted diseases）の略が普及しているが，多くの性感染症において無症候性感染者がキャリアとなって感染拡大に大きく関与していることが指摘されるようになり，性感染症をsexually transmitted diseasesではなく，sexually transmitted infection：STIと呼ぶようになっている．

耳鼻咽喉科医も性感染症に適切な対応を

- 咽頭に病変を生じる性感染症（sexually transmitted infection：STI）[★1]には，梅毒，単純ヘルペスウイルス（herpes simplex virus：HSV）感染症，ヒト免疫不全ウイルス（human immunodeficiency virus：HIV）感染症，淋菌感染症，クラミジア感染症がある．
- 咽頭梅毒は，他の疾患にはみられない特徴的な病変を呈する．
- 単純ヘルペスウイルス初感染者の一部は，口腔・咽頭粘膜に特徴的なアフタ・びらん・白苔を伴う咽頭炎や偽膜性扁桃炎を発症する．
- HIV感染症は感染から2～4週間目ごろ，約50％の感染者にインフルエンザまたは伝染性単核球症様の症状とともに，非特異的な咽頭炎が生じる．
- 淋菌の咽頭感染とクラミジアの咽頭感染は，その大多数は無症候性感染であるが，一部の感染者に非特異的な咽頭炎，扁桃炎，上咽頭炎がみられる．

梅毒

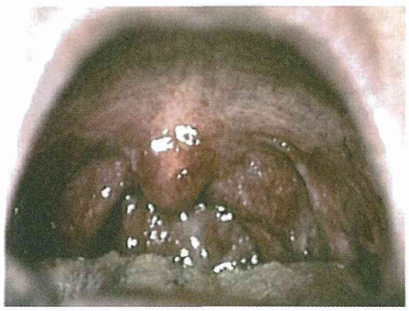
- 梅毒はスピロヘータの一種である梅毒トレポネーマ（*Treponema pallidum* subspecies *pallidum*：以下*Tp*）を病原体とする慢性感染症[1]で，体のあらゆる部分または全身の皮膚や粘膜，時に臓器に病変を生じる[★2]．
- 梅毒は*Tp*に感染してからの時期によって第1～4期に分けられ，それぞれの病期によって現れる病変が異なる．
- 第1～2期（感染から約2年間）は早期梅毒といい，病変や血液中の*Tp*の量が多く，他者への感染性をもち，血清抗体価が高値を示す[★3]．第3期以降は晩期梅毒といい，未治療でも他者への感染力はなくなり血清抗体価も低値となる．

★2
皮膚・粘膜や臓器に病変がみられる顕症梅毒に対して，第1～4期を通じて症状や病変を欠く場合を潜伏梅毒という．

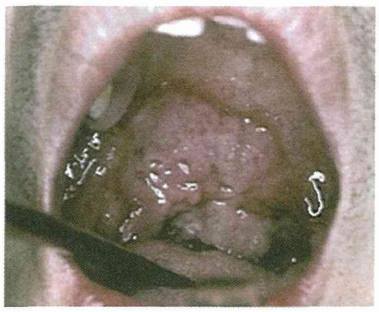
★3
潜伏梅毒でも第1～2期の早期は他者への感染源となる．

Topics　性行動の多様化と口腔咽頭の性感染症

性行動の多様化に伴い咽頭を介して性感染症に感染する人の増加がクローズアップされている．厚生労働省の性感染症に関する特定感染症予防指針では，「性感染症が口腔を介した性的接触で感染する」ことが2012年1月に追記された．また同省は性感染症の啓蒙活動の一環として設けている「性の健康週間」（毎年11月25日～12月1日）で，2012年は「オーラルセックスによる性感染症」をトピックスとして取り上げ，HPにオーラルセックスによる性感染症に関するQ&Aや啓蒙用ポスターが掲載されている．そのほか，さまざまなメディアからも口腔咽頭の性感染症に関する情報が数多く発信されるようになり，性感染症の相談を目的に耳鼻咽喉科を受診する人は今後確実に増加するであろう．性感染症は都市部，地方にかかわらず普遍的な疾患であり，性感染症に適切に対応できることが耳鼻咽喉科医に求められている．



❶梅毒性紅斑（53歳，男性）
咽頭の粘膜病変は，はじめ紅斑として現れ，紅斑から徐々に拡大して白色の粘膜斑に変化する．



❷梅毒2期の咽頭粘膜斑（43歳，男性）
口蓋垂から口蓋粘膜に拡大した粘膜斑．粘膜斑は扁平で若干の隆起があり，周囲は薄い赤色の紅暈で囲まれ青みがかった白灰色で「乳白斑」ともよばれる．
（荒牧　元．口腔咽頭粘膜疾患アトラス．医学書院：2001．p.51[2]より）

咽頭梅毒の臨床所見

- 咽頭に現れる梅毒病変には，第1期の初期硬結，硬性下疳，第2期の粘膜斑がある[1-4]．
- 初期硬結，硬性下疳，粘膜斑は，その特徴的な所見から他の疾患との鑑別は比較的容易である．

第1，2期の咽頭梅毒病変は，その特徴的所見から他患者との鑑別は比較的容易

初期硬結・硬性下疳★4

- 性的接触によって *Tp* が直接侵入した部位に，感染から約3週間後ころに現れる．
- 性器，次いで口腔・咽頭に好発する．
- 口腔・咽頭では，口唇，舌，扁桃，軟口蓋の順に多い．
- 初期硬結は，アズキ大から指頭大の大きさで，軟骨のように硬い暗赤色のしこりとして現れる．
- 初期硬結は数日後に自潰する．これを「硬性下疳」という．
- 通常，初期硬結，硬性下疳は単発性の病変★5で，病変と同側の頸部リンパ節腫脹★6を伴う．
- 初期硬結・硬性下疳は痛みを伴わず，3～6週間で自然消退する★7．

★4
第1期病変の好発部位は性器，次いで多いのが口腔・咽頭である．

▶「口腔における性感染症」の項（p.30）参照．

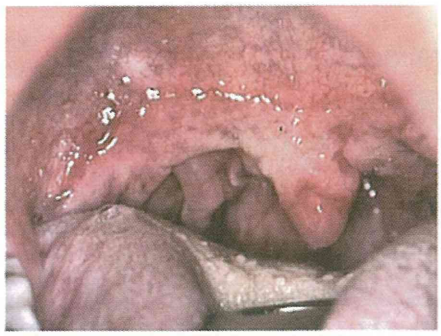
★5
症例数は少ないが，病変が2～3個現れる場合もある．

★6
初期硬結，硬性下疳と同じく軟骨様の硬さで腫脹する．

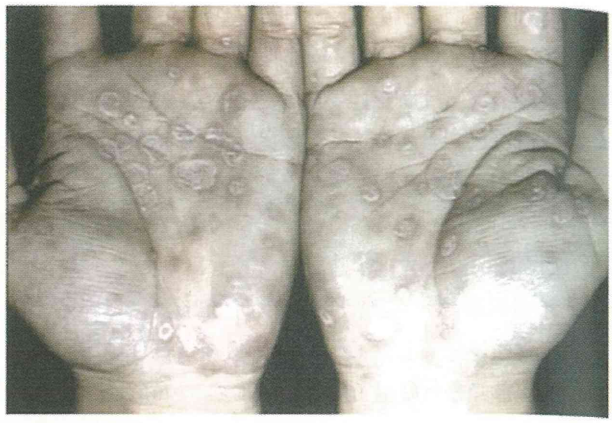
★7
疼痛などの自覚症状に乏しく，自然に消退するため，この時点で医療機関を受診する顕症梅毒患者は少ない．

粘膜斑

- 感染から約3週間～2年前後の第2期，血行性に *Tp* が全身に広がって現れる多彩な皮膚・粘膜病変の一つとして生じる．
- 最初は紅斑（❶）として現れ，徐々に白くなり変化しながら拡大・融合して，粘膜斑になる．
- 周囲を薄い赤色の紅暈で囲まれ青みがかった白または灰色で，扁平で若干隆起のある病変（❷）で，「乳白斑」とも称される．



❸梅毒２期の咽頭粘膜斑（27歳，女性）
粘膜斑が口峡部に沿って弧状に拡大融合して，チョウが羽を広げたような“butterfly appearance”を呈している．
（荒牧　元ほか．JOHNS 1993[3]より）



❹梅毒性乾癬（21歳，男性）
赤く湿潤し鱗屑を伴う，乾癬に類似した特徴的な梅毒疹．発現頻度が高い皮疹で，角層の厚い手掌や足底に生じる．丘疹性梅毒疹の亜型．
（余田敬子．JOHNS 2007[5]より）

▶「口腔における性感染症」の項（p.30）参照．

★8
咽頭梅毒特有の所見で，頻度の高い病変である．

★9
出現頻度が高い皮疹は梅毒性乾癬と丘疹性梅毒疹で，続いて梅毒性バラ疹，扁平コンジローム，梅毒性脱毛が多く，膿疱性梅毒疹は比較的少ない．

★10
*Tp*は分離培養ができない．

- 好発部位は扁桃，口蓋弓，軟口蓋，口蓋垂で，口唇粘膜，歯肉，舌側裏面にも生じる．
- 口峡部粘膜，とくに軟口蓋の後縁に沿って弧状に拡大融合すると，チョウが羽を広げたような形態“butterfly appearance”★8（❸）を呈する．
- 咽頭梅毒患者は，第２期の皮膚病変★9や性器病変を併発する場合もあるが，むしろ性器や皮膚に病変がなく咽頭病変のみで耳鼻咽喉科を受診する場合のほうが多い[4]．

咽頭梅毒の診断

- 梅毒の診断には*Tp*★10を病変部から採取したスワブを鏡検する直接法と，

Column　第２期梅毒の皮膚病変

第２期症例では多彩な皮膚病変がみられる．口腔咽頭の粘膜病変を呈する症例にこれらの皮膚病変を同時に認めた場合，梅毒を強く示唆する根拠となる[2-4]．

①梅毒性バラ疹：第２期の最も早い時期に生じる．爪甲大までの淡紅色斑で，体幹・上肢に対称性に出現する．かゆみなどの自覚症状はなく，数週で消退するため見過ごされることが多い．

②丘疹性梅毒疹：バラ疹に遅れて現れる暗赤色の丘疹ないし結節．

③梅毒性乾癬：角層の厚い手掌や足底に生じる，赤く湿潤し鱗屑を伴う乾癬に類似した皮疹（❹）[5]．出現頻度が高く梅毒に特徴的な臨床所見を呈するため，梅毒診断の契機となりやすい．

④扁平コンジローム：疣状または扁平に隆起して表面は顆粒状，湿潤・浸軟し淡紅色から灰白色の小腫瘤．肛門周囲・外陰部・腋窩など汗分泌が多い皮膚間擦部に生じ，病変からは*Tp*が多数検出され感染源となりやすい．

⑤梅毒性脱毛：びまん性と小斑状に分けられ，前者は前頭部または側頭部の，後者は後頭部に散発する爪甲大の脱毛で，いずれも患部の毛髪を約1/2残す不完全脱毛を呈する．

⑥膿疱性梅毒疹：大小種々の多発性膿疱．その形態に応じ，梅毒性痤瘡・梅毒性膿痂疹・梅毒性膿瘡とよぶ．全身状態が不良または免疫不全の場合にみられる場合が多く[3]，これを認めた場合にはHIV感染の合併に留意する．

梅毒血清反応とがある.

- 咽頭梅毒の病変には *Tp* が多く存在するため直接法[★11]は有用である.
- 梅毒血清反応は血行性感染が始まる第2期以降の診断に有用である.
- 血清梅毒反応陰性でも，問診や臨床所見から第1期が疑われる場合は，1～2か月後に再検査を行う.

咽頭梅毒の治療

- 第一選択薬はペニシリンであるが，*Tp* はほとんどの抗菌薬に感受性がある．診断に先行したむやみな抗菌薬の投与は病変のみが消失して見逃され，潜伏梅毒に移行させてしまうおそれがあるため注意する.
- 経口合成剤（AMPC〈アモキシシリン水和物〉，ABPC〈アンピシリン水和物〉など）を1回500 mg，またはDBECPCG（ベンジルペニシリンベンザチン水和物；バイシリンG®）1回40万単位，を1日3回投与する.
- ペニシリンアレルギーの場合は，ミノサイクリン塩酸塩を1回100 mg，1日2回投与する.
- 第1期では2～4週間，第2期では4～8週間[★12]投与する.
- 治療開始直後の2～12時間後に現れる，ヤーリッシュ・ヘルクスハイマー（Jarisch-Herxheimer）反応[★13]に注意する.
- 治療効果の評価は，臨床症状とSTSの抗体価による.

単純ヘルペスウイルス感染症

- 単純ヘルペスウイルスには，1型（HSV-1）と2型（HSV-2）がある.

★11
硬性下疳をもみだす，粘膜斑の表面を擦るなどして漿液を採取してスライドクラスにとり，染色し観察する．長さ6～20 μmで8～20のらせんをもつ病原体を確認し，診断する．ただし，*Tp* と口腔内常在性トレポネーマとの鑑別は困難で，臨床所見や梅毒血清反応と合わせて診断する．*Tp* はほとんどの抗菌薬に感受性があるため，いったんなんらかの抗菌薬が投与されるとすみやかに病変部から *Tp* が消えてしまうため，抗菌薬投与前に行うことが肝要である.

★12
梅毒の治療は臨床病期により投薬期間が異なる.

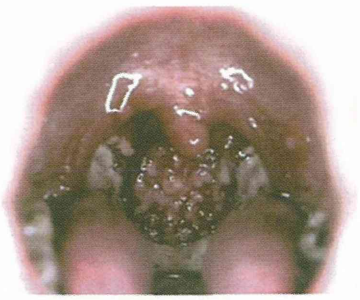
★13
治療に際し，開始直後の2～12時間後に悪寒戦慄・発熱・倦怠感・咽頭痛・筋肉痛・頭痛・頻脈などの症状が，一過性に現れ，1日経たずに消失する．これをヤーリッシュ・ヘルクスハイマー反応といい，*Tp* が多量に死滅することによるエンドトキシン反応と考えられている．第1期で約50 %，第2期では約75 %にみられる．投薬開始時にこの現象をあらかじめ説明し，患者さんが薬の副作用と誤って服用を中断しないよう指導する必要がある.

Column　血清梅毒反応

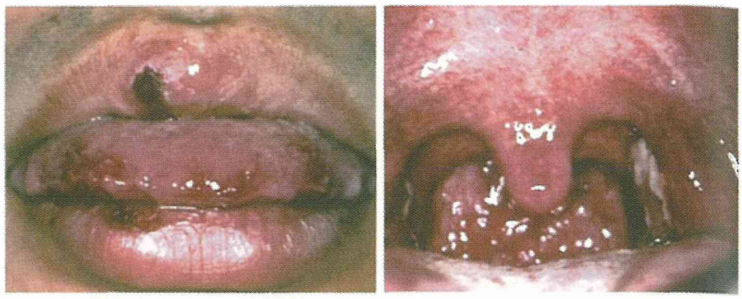
梅毒血清反応には，リン脂質のカルジオリピンを抗原とする脂質抗原試験（serologic test for syphilis：STS）と，*Tp* 抗原法がある．STSにはガラス板法やRPR(rapid plasma reagin)があり，*Tp* 抗原法にはTPHA(*Treponema pallidum* hemagglutination assay：梅毒トレポネーマ感作赤血球凝集試験）とFTA-ABS（fluorescent treponemal antibody absorption test；梅毒トレポネーマ蛍光抗体吸収試験）法がある．はじめにSTSの2法とTPHA定性検査を行い，陽性の場合にSTSおよびTPHA定量検査で確定診断する．これまで用手法で行われていたSTSおよびTPHA定量検査は，近年高感度の自動定量測定装置が開発され，各医療施設に導入されつつある．自動定量測定と従来の用手法による定量検査の数値の相関性は自動測定キットのメーカーにより異なるので注意する.

STSは感染後3～4週して陽性となる．妊娠やその他の感染症などで疑陽性反応が生じることがあり（生物学的偽陽性），STSの陽性者には *Tp* 抗原定量検査による確認が必要となる．*Tp* 抗原はSTS陽転後2～3週遅れて陽性となる.

治療後，体内の *Tp* が消失するとSTS抗体価は下がりはじめるので，STS定量値は治療効果判定に用いられる．TPHA定量値は治療後に必ずしも低値にならず，治療効果を反映しない．病期に応じた十分な投薬を行った後，臨床症状の持続や再発がないことと，STS抗体価を定期的に追跡して定量値が8倍以下に低下するまで確認する必要がある．治療後半年過ぎてもSTS定量値が16倍以上示す例は，治療が不十分または再感染例が疑われ，検査と治療を追加する.



❺HSV 咽頭扁桃炎（20 歳，女性）
口蓋扁桃陰窩の白苔，咽頭後壁リンパ濾胞の白苔を伴う発赤腫脹を認める．（余田敬子ほか．日本扁桃研究会会誌 1993[6] より）



❻HSV 扁桃炎（25 歳，男性）
血清抗体価および扁桃組織生検により，HSV-1 初感染による扁桃炎と診断された．偽膜性扁桃炎にアフタを伴う歯肉口内炎の併発がみられる．

★ 14
症例数は少ないが，HSV-1 による性器ヘルペスや，HSV-2 による口唇ヘルペスもある．

- HSV-1 は主に口唇・顔面・眼に病変を生じ，2 型は主に性器に病変を生じる★14．
- HSV-1，HSV-2 ともに，初感染の 90％以上は不顕性感染し，潜伏感染に移行する．
- 初感染者の約 10％に，歯肉口内炎，咽頭・扁桃炎，性器ヘルペスの発症がみられる．

HSV 咽頭扁桃炎の臨床所見

- 10 歳代後半から 30 歳代前半の青壮年期に好発する．
- HSV 未感染者が，キスやオーラルセックスなどで口腔咽頭から HSV を含む唾液や体液に曝露されて初感染した人の一部に発症する．
- HSV-1，HSV-2，どちらも原因となる[6]．
- 39℃前後の弛張熱，上頸部リンパ節の高度腫脹，白苔を伴う扁桃炎を伴って伝染性単核症とよく似た臨床像を呈する場合が多い（❺）．
- 咽頭痛の程度は強く，摂食障害をきたす場合が多い．
- 口腔粘膜や口唇にヘルペス特有のアフタを伴うことが多い（❻）．
- 性器ヘルペスや皮膚のヘルペス疹を同時に認めることもある．

Topics　梅毒と HIV の混合感染

わが国におけるここ 30 年ほどの梅毒患者数は，1987 年の 2,928 例をピークに以後減少し続け，1997 年には最少の 445 例となった．しかし，2004 年を境に患者数が微増に転じ，20～45 歳の男性に増加傾向がみられ，新規 HIV 感染者との関連が指摘されている．

先進諸国の梅毒陽性者には HIV 感染者が多く，わが国も例外ではない．わが国における HIV 感染者および AIDS 患者は 20～40 歳代の男性同性愛者が圧倒的に多く，そのため梅毒と HIV の同時陽性者も 20～40 歳代の男性に多い．HIV 感染者では顕性梅毒が多く，また梅毒の再感染や再発も多い．また，非典型な梅毒疹がみられる例，出現する症状が病期の順序どおりでない例，通常ではない早さで進行する例，早期から神経梅毒を発症する例の報告がある．梅毒血清反応の定量値も，異常な高値または低値を示したり，激しく変動したりする．治癒が遷延する症例もあり長い経過観察が必要となる．

- 口腔・咽頭の帯状疱疹と鑑別を要するが，帯状疱疹は正中を越えず一側性のことが多い．

診断

- 保険で認められた検査[★15]で迅速に確定診断することは難しく，臨床症状，問診，視診から総合的に診断する．
- HSV 咽頭扁桃炎であれば，抗ウイルス薬の投与開始 3 日目ごろから劇的な症状の改善がみられる．

治療

- バラシクロビル塩酸塩 1 回 500 mg，1 日 2 回を経口で 5 日間，またはアシクロビル 1 回 200 mg，1 日 5 回を経口で 5 日間投与する．
- 経口摂取困難な重症例では，アシクロビル注 5 mg/kg/回，1 日 3 回 8 時間ごと，7 日間投与する．
- 腎機能障害合併例では，❼[7]に従い，クレアチニンクリアランス値（Ccr）により投与量を決定する．
- HSV または VZV 初感染では，可及的早期に十分量の抗ヘルペスウイルス薬で治療することが重要であるため，臨床的に HSV 感染症が強く疑われたら，迷わず抗ヘルペスウイルス薬の投与を直ちに開始する[★16]べきである．
- 抗ウイルス薬投与を開始した後，改善の兆しが現れるまで通常 3 日ほどかかる．5 日目になっても軽快しない，あるいはむしろ悪化する場合には，細菌の二次感染の併発または他の疾患を考えた治療に切り替える．

★15
現在，HSV 感染症の診断に有用な検査としてあげられるもの（Column 参照）のうち，保険で適用されるのは蛍光抗体法と血清抗体検査のみである．

★16
初感染でとくに症状や病変が著しい症例には，十分量の抗ウイルス薬治療を早期から開始することで，潜伏感染するウイルス量を減らし，その後の再発回数を抑制できることが指摘されている．抗ヘルペスウイルス薬のアシクロビル，バラシクロビル塩酸塩は，HSV-1，HSV-2，VZV 感染細胞にのみ作用するため，重篤な副作用はほとんど生じない．

Column HSV 感染症の検査

口腔咽頭領域の HSV 感染症は，経験を有する耳鼻咽喉科医であれば臨床所見，症状，経過からほとんどの症例で診断可能である．重篤化のおそれがある移植後患者などで臨床的に他の疾患との鑑別診断が困難である場合は，下記の方法で咽頭の病変から採取した擦過細胞や生検組織から HSV 感染の証拠を検索する．

①ウイルス分離培養：ゴールドスタンダード．特異性が高く，型判定が可能．

②核酸増幅法（PCR 法）：特異性が高く型判定が可能．

③抗原検査（モノクローナル抗体による蛍光抗体法）：簡便で，迅速に結果が得られる．特異性高く型判定が可能．綿棒で擦過採取したアフタや潰瘍病変の細胞をスライドグラスに塗抹し，抗 HSV-1 および抗 HSV-2 モノクローナル抗体を用いて，ウイルス感染細胞を同定する．

④ツァンク（Tzanck）試験：外来で迅速簡便に検査が可能，感染細胞に特徴的な full 型または Cowdry 型の核内封入体，またはウイルス巨細胞を確認する．HSV と水痘・帯状疱疹ウイルス（varicella-zoster virus：VZV）の判別は不可．

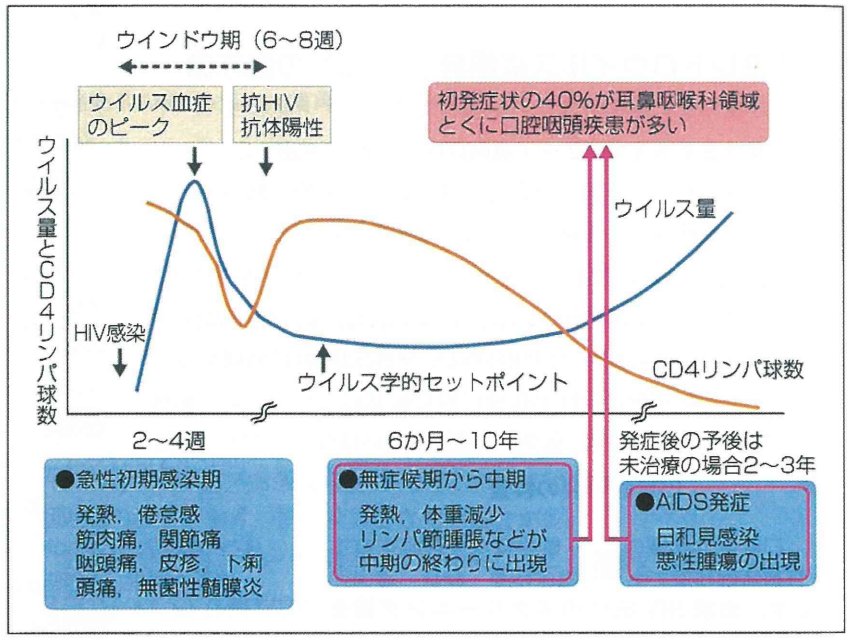
⑤血清抗体検査：単回検査では臨床的意義が低い．急性期と回復期のペア血清で有意の抗体上昇によって診断することが可能である．HSV 初感染後は生涯持続感染するので，血清抗体価が陽性であることだけでは診断的意味はない．HSV は同一個体において HSV-1 初感染，HSV-2 初感染，潜伏持続感染，再発といったさまざまな病態があり，また HSV-1 と HSV-2，また HSV と VZV 間で交叉反応が存在するため，血清抗体価から HSV-1，HSV-2，VZV を判別できない場合もある．

❼腎機能障害患者におけるHSV感染症のアシクロビルの用量

クレアチニンクリアランス	アシクロビル錠（1回200 mg）	バラシクロビル錠（1回500 mg）	アシクロビル注射用
25 mL</分	1日5回		12時間ごと5 mg/kg
10～25 mL</分	1日5回		24時間ごと5 mg/kg
<10 mL</分	1日2回		24時間ごと2.5 mg/kg
30<～ mL</分		1日2回	
15～35 mL</分		1日2回	
<15 mL</分		1日1回	

・血清クレアチニン値からクレアチニンクリアランスを推定する計算式
男性　体重(kg)×[140－年齢]/[72×血清クレアチニン値(mg/dL)]
女性　男性の計算式×0.85

（本田まりこ．Medical Practice 2011[9]より）



❽HIV-1感染症の自然経過
（IDWR感染症発生動向調査週報　感染症の話．2002年第40週号(2002年9月30日～10月6日)掲載　後天性免疫不全症候群(後編)．http://idsc.nih.go.jp/idwr/kansen/k02_g2/k02_40/k02_40.html　掲載の図に赤矢印部分を追加）

Column　HIV-1感染症の自然経過（❽）

HIV-1に感染すると2～4週間で，血中のHIVウイルス量は急速にピークに達し，ARSの症状が出現する．感染から6～8週後，血中に抗体が産生されはじめ，ピークに達していたウイルス量が減少し，一定のレベルの定常状態となり，無症候期に入る．無症候期を過ぎ，CD4リンパ球数が減少し始めるとAIDSを発症する．

❾HIV感染に関連する口腔病変

感染症	真菌感染，細菌感染，ウイルス感染
新生物	カポジ（Kaposi）肉腫，非ホジキン（Hodgkin）リンパ腫，扁平上皮癌
炎症性	再発性アフタ性口内炎，多形紅斑，苔癬
原因不明	唾液腺疾患，非特異的口腔潰瘍，メラニン色素の過度の沈着

（田上　正．化学療法の領域2006[8]より）