

# Antibiotic treatment of Shiga toxin-producing *Escherichia coli* related gastroenteritis and the risk of hemolytic uremic syndrome: a population based matched case-control study in Japan

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### Background

The role of therapeutic intervention, particularly antibiotics, for Shiga toxin-producing *Escherichia coli* (STEC) related infection is controversial.

## Methods

- A population based matched case-control study to assess the association between treatment (antibiotics, antidiarrheal agents and probiotics) for STEC related infections and hemolytic uremic syndrome (HUS) development.
- We identified all STEC HUS patients as cases and matched five non-HUS patients as controls using the data from the National Epidemiological Surveillance of Infectious Diseases (NESID) between January 1, 2017, and December 31, 2018.
- Further medical information was obtained by standardized questionnaires answered by physicians who registered each patient.
- We used multivariate conditional logistic regression model to evaluate the association between exposures (use of antibiotics, use of antidiarrheal agents, use of probiotics, by matched odds ratios (OR) and 95% confidence intervals (CI).
- Covariates we used were sex, age group, area code, presence of diarrhea and other factors. We also performed subgroup analyses using age (adults and children) as a stratification factor.



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Table. Baseline characteristics of cases and controls in the analysis dataset

			Cases (n=90)	Controls (n=371)	
			No. /total No. (%)	No. /total No. (%)	p value
mptoms					
	Vomiting		50/87 (57.5)	68/365 (18.6)	< 0.001
	Diarrhea		85/89 (95.5)	355/370 (95.9)	0.772
	Abdominal pai	in	75/84 (89.3)	288/347 (83.0)	0.183
	Fever		69/88 (78.4)	140/365 (38.4)	< 0.001
	Bloody stool		74/89 (83.1)	305/370 (82.4)	1
		Mild	12/61 (19.7)	107/278 (38.5)	0.005
		Moderate	25/61 (41.0)	134/278 (48.2)	0.325
		Severe	24/61 (39.3)	37/278 (13.3)	< 0.001
EC					
	Positivity of stool culture		54/90 (60.0)	363/367 (98.9)	< 0.001
	Shiga toxin	Stx 1	23/62 (37.1)	246/367 (67.0)	< 0.001
		Stx 2	44/62 (71.0)	210/367 (57.2)	0.05
		Type unknown	7/62 (11.3)	36/367 (9.8)	0.653
	Serotype	0157	65/79 (82.3)	216/365 (59.2)	< 0.001
		026	0/79 (0.0)	89/365 (24.4)	< 0.001
		0103	2/79 (2.5)	13/365 (3.6)	1
		0111	1/79 (1.3)	15/365 (4.1)	0.325
		Others	11/79 (13.9)	32/365 (8.8)	0.205
Anti-verotoxin antibody			34/36 (94.4)	23/30 (76.7)	0.068
alysis			27/85 (31.8)		-
nical outcome		Cured	72/85 (84.7)	354/357 (99.2)	< 0.001
		Any complication	10/85 (11.8)	2/357 (0.6)	< 0.001
		Encephalopathy	13/89 (14.6)		-
		Death	3/85 (3.5)	0/357 (0.0)	0.007
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					Matched UR (95% CI)		Matched UR (95% CI)	
	Variables	Cases	Controls	<ul> <li>Adjusted</li> </ul>	Unadjusted	p-value	Adjusted	p-value
All ages	Any antibiotics	58/90	275/360		0.65 (0.42-1.02)	0.060	0.72 (0.45-1.15)	0.170
	Fosfomycin	37/90	205/360		0.52 (0.33-0.81)	0.004	0.75 (0.47-1.20)	0.226
	Quinolones	5/90	40/360		0.61 (0.23-1.59)	0.309	0.83 (0.30-2.30)	0.721
	Macrolides	3/90	17/360	•	0.83 (0.26-2.65)	0.756	0.60 (0.18-2.02)	0.409
	Beta-lactams	25/90	43/360	••	2.47 (1.54-3.98)	<0.001	1.33 (0.79-2.22)	0.283
	Antidiarrheal agents	13/85	16/341		2.54 (1.37-4.72)	0.003	2.07 (1.07-4.03)	0.031
	Probiotics	70/84	304/347		0.69 (0.38-1.25)	0. 220	0.86 (0.46-1.61)	0.639
Children	Any antibiotics	40/68	204/257		0.46 (0.28-0.75)	0. 002	0.56 (0.32-0.98)	0.041
	Fosfomycin	28/68	181/257		0.38 (0.23-0.62)	<0.001	0.58 (0.34-1.01)	0.063
	Quinolones	0/68	7/257		- *	- *	- *	- *
	Macrolides	3/68	10/247		1.18 (0.37-3.79)	0.783	0.97 (0.27-3.42)	0.960
	Beta-lactams	16/68	23/257	<b>_</b>	2.27 (1.29-4.02)	0.005	1.11 (0.59-2.10)	0.739
	Antidiarrheal agents	9/63	9/242	•	2.96 (1.43-6.12)	0.004	2.65 (1.21-5.82)	0.015
	Probiotics	52/62	223/246		0.60 (0.30-1.21)	0.153	1.00 (0.48-2.09)	0.994
Adults	Any antibiotics	18/22	71/103		2.17 (0.73-6.45)	0. 163	1.57 (0.46-5.39)	0. 477
	Fosfomycin	9/22	24/103	<b>+</b> •+	1.70 (0.72-4.01)	0.224	1.40 (0.51-3.88)	0.512
	Quinolones	5/22	33/103	<b>_</b>	0.79 (0.29-2.15)	0.637	1.07 (0.35-3.23)	0.905
Na Be Antidiarrheal agents	Macrolides	0/22	7/103		- *	- *	- *	- *
	Beta-lactams	9/22	20/103		3.06 (1.26-7.46)	0.014	1.88 (0.69-5.14)	0.219
	Antidiarrheal agents	4/22	7/99	÷	<ul> <li>1.84 (0.59–5.76)</li> </ul>	0.294	1.84 (0.32-10.53)	0.494
	Probiotics	18/22	81/101	••	0.93 (0.31-2.79)	0. 902	0.76 (0.21-2.71)	0.666
			0	12 0.25 0.50 1.0 2.0 4.0 8	<b>1</b>			

### Conclusion

- Fosfomycin might decrease the risk of HUS in children younger than 15 years of age with STEC confirmed bacterial gastroenteritis.
- Antidiarrheal agents are clear risk factor of HUS regardless of ages.

## **Contact Address**

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Figure 2. Conditional logistic regression analysis to evaluate the association between treatment and development of HUS