

LKS Faculty of Medicine Department of Medicine

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Introduction

Recent studies suggested that antibiotics may modulate colorectal cancer (CRC) risk due to gut dysbiosis. We aimed to investigate the effects of different antibiotics on CRC development in older subjects.

Methodology

This was a retrospective cohort study based on a territory-wide healthcare database (CDARS) in Hong Kong. All patients aged ≥60y who had undergone index diagnostic or screening colonoscopy with no CRC diagnosed between 2005 and 2013 were recruited. Exclusion criteria included inflammatory bowel disease, prior colectomy, prior CRC and CRC detected within 6m of index colonoscopy.



Figure. Patient selection flow diagram

<u>Primary outcome</u>: CRC that developed >6m after index colonoscopy **Observation:** CRC diagnosis, death or end of study (31 December 2017) **Exposure:** any antibiotic use up to 5y before index colonoscopy (11 classes of antibiotics – penicillins, cephalosporins, macrolides, carbapenems, quinolones, tetracyclines, aminoglycosides, nitroimidazoles, glycopeptides, sulpha/trimethoprim, and others (clindamycin, nitrofurantoin, linezolid, rifampicin, rifaximin, and daptomycin). Covariates: refer to Table 1

Statistical analysis: Multivariable Cox proportional hazards \rightarrow adjusted hazard ratio (aHR) of CRC with antibiotics Stratified analysis:

- **Proximal colon** [from cecum to transverse colon] vs **distal colon** [from splenic flexure to sigmoid colon) vs **rectum**
- **Duration** (nonuse, < 2weeks, ≥ 2 weeks)
- **Nature of antibiotics** (anti-anaerobic vs anti-aerobic, broad vs narrow spectrum, and oral vs intravenous)

Association between antibiotic usage and colorectal cancer development: a territory-wide study

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Table 1. Characteristics of antibiotic users and non-users

	All	Antibiot	tic users	Antibiotic non-users		No.of patients and events	aHR	95% CI	P-value		No. of patients and events	aHR*	95% CI	p-value	
	(n=97,162)	(n=58,	3,704)	(n=38,458)	Rectum (n=96,737, event	t= 601)									
Age at index colonoscopy	71.4 (65.1 – 77.8)	72.7 (66.1	1 – 78.9)	69.5 (64.0 – 75.8)	Anti-anerobic vs anti-aero	obic activity	Rectum (n=96,737, event=601)								
(years)		20625 (1	(52.20/)	20216 (52.6%)	Nonuse	n=38 322: event=287	Ref		_			_			
History of colonic polyns (n	29662 (20 5%)	30625 (: 19666 (:	(27.2%)	20216 (52.6%)		n=50,322, event=207	0.64	0.53 - 0.76	< 0.001	Nonuse	n=38,372; event=287	Ref	-	-	
	29003 (30.3%)	13000 (/	27.270)	9997 (20.078)		n=8 034: event=43	0.69	0.03 - 0.70	0.001	< 2 weeks	n=21,587; event=127	0.73	0.59 – 0.91	0.004	
Polypectomy at index	16087 (16.6%)	10027 (10027 (17.1%) 6060 (15.8%)		Broad vs parrow spectrur	n activity	0.08	0.49 - 0.95	0.017						
colonoscopy (n. %)					Nonuse	n=38 322: event=287	Rof	_	_	$ \geq 2 \text{ weeks} n=36,828; \text{ event}=187 0.58 0.48 - 0.71 <$					
Smoking (n. %)	3637 (3.7%)	3332 ((5.7%)	305 (0.8%)	Broad-spectrum	n=58,522, event=287	0.63	0.53 - 0.75	< 0.001	Proximal colon (n=9	96,307, event=171)			1	
Alcohol (n, %)	495 (0.5%)	389 (0	0.7%)	106 (0.3%)		11-34,872, event-234	0.03	0.33 - 0.73	< 0.001						
DM (n, %)	11442 (11.8%)	10533 (2	(17.9%)	909 (9.1%)	Narrow-spectrum	n=3,543; event=20	0.77	0.49 – 1.22	0.277	Nonuse	n=38,080; event=45	Ref	-	-	
Hypertension (n, %)	23512 (24.2%)	17468 (2	(29.8%)	6044 (15.7%)	Oral vs intravenous antib			1		< 2 weeks	n=21,509; event=49	1.73	1.15 – 2.60	0.008	
Dyslipidemia (n, %)	7290 (7.5%)	5112 (8	(8.7%)	2178 (5.7%)	Nonuse	n=38,322; event=287	Ref	-	-						
AF (n, %)	5029 (5.2%)	4098 ((7.0%)	931 (2.4%)	Oral	n=34,690; event=178	0.65	0.54 – 0.78	< 0.001	\geq 2 weeks	n=36,718; event=77	1.57	1.07 – 2.30	0.021	
IHD (n, %)	11141 (11.5%)	8394 (1	14.3%)	2747 (7.1%)	Intravenous	n=3,481; event=23	0.77	0.50 – 1.18	0.237	Distal colon (n=96.3	290 event-254)				
CHF (n, %)	5737 (5.9%)	5045 (8	(8.6%)	692 (1.8%)	Oral + intravenous	n=20,244; event=113	0.60	0.47 – 0.76	< 0.001						
Stroke (n, %)	6541 (6.7%)	5066 (8	(8.6%)	1475 (3.8%)	Proximal colon (n=96,307	, event=171)				Nonuse	n=38,126; event=91	Ref	-	-	
CRF (n, %)	2986 (3.1%)	2664 (4	(4.5%)	322 (0.8%)	Anti-anaerobic vs anti-ae	robic activity									
Cirrhosis (n, %)	696 (0.7%)	593 (1	1.0%)	103 (0.3%)	Nonuse	n=38,080; event=45	Ref	-	-	< 2 weeks	n=21,512; event=52	0.92	0.65 – 1.30	0.634	
Dementia (n, %)	1225 (1.3%)	1084 (:	(1.8%)	141 (0.4%)	Anti-anaerobic	n=50,222; event=112	1.69	1.18 – 2.41	0.004	\geq 2 weeks	n=36,752; event=111	1.04	0.78 - 1.40	0.786	
Parkinsonism (n, %)	726 (0.7%)	585 (1	1.0%)	141 (0.4%)	Anti-aerobic	n=8,005; event=14	1.33	0.73 – 2.43	0.354						
Aspirin (n, %)	22004 (22.6%)	15864 (2	(27.0%)	6140 (16.0%)	Broad vs narrow spectrur	n activity									
NSAIDs (n, %)	8000 (8.2%)	5649 ((9.6%)	2351 (6.1%)	Nonuse	n=38.080: event=45	Ref	_	_						
COX-2 inhibitors (n,%)	108 (0.1%)	71 (0.).1%)	37 (0.1%)	Broad-spectrum	n=54 695: event=117	1.60	1 13 - 2 29	0.009	Results					
Statins (n,%)		11629 (3	(19.8%)	6022 (15.7%)	Narrow spectrum	n=2 E22: ovent=0	2.00	1.13 2.23	0.005						
Annual center endoscopy	2892	285	92	2887	Oral vs introvenous antih		2.00	1.02 - 4.27	0.045	- 97,162 (male:	50,841 [52.3%]); median a	ge at inde	ex colonoscopy:	71.4 years	
volume	(2045 – 3316)	(2054 – 3316)		(2033 – 3291)	Oral vs intravenous antib		Def	T		(IQR:65.1–77.8)) (Table 1)				
Annual center polypectomy	24.6%	24.6%		24.7%	Nonuse	n=38,080; event=45	Ret .	-	-	- Median duration of antibiotic use: 15 days (IQR:7–31)					
rate*	(21.7% - 28.2%) (21.7% - 28.0%)		(21.6% - 28.4%)	Oral	n=34,580; event=68	1.53	1.05 – 2.24	0.028	- Pre-colonoscopy antibiotics were associated with lower rectal canc						
					Intravenous	n=3,470; event=12	2.61	1.37–4.97	0.004	$(a \square K. 0.04, 95\%$ $(1.0.54 - 0.76)$ but nigner proximal colon cancer risk					
					Oral + intravenous	n=20,177; event=46	1.65	1.07 – 2.56	0.024	(aHR:1.62;95%CI:1.14–2.30); while there was no significant association between					
Table 2. Association betw	een antibiotics and C	RC after ind	lex colonos	copy negative for CRC	Distal colon (n=96,390, event=254)					antibiotics and distal colon cancer (aHR:0.99;95% CI:0.76–1.30) (Table 2)					
Nun	nber of patients and	aHR*	95% CI	p-value	Anti-anaerobic vs anti-ae	robic activity	- Dimerential effects of antibiotics on CRC according to their (1) anti-anaerobic vs								
	events				Nonuse	n=38,126; event=91	Ref	-	-	anti-aeropic act	Ivity, (2) broad-spectrum vs n	arrow spe	ctrum activity, and	a (3) orai vs	
Rectum (n=96,737, event=601)				Anti-anaerobic	n=50,252; event=142	0.99	0.75 – 1.31	0.944		both route (I able 3)					
Nonuse n=	38,372; event=287	Ref	-	-	Anti-aerobic	n=8,012; event=21	1.02	0.63 - 1.64	0.944				and ≥z weeks was	s 0.73 (95%	
Any antibiotic use n=	58,480; event=314	0.64	0.54 - 0.76	< 0.001	Broad vs narrow spectrur	n activity	•		•	cancer aHRs	was $1.73 (95\% \text{ CI.0.46-0.71})$), respect	57 (95% CI-1 0	$7_2 30)$ for	
					Nonuse	n=38,126; event=91	Ref	-	-	antibiotic use <	was 1.75 (357) Ol.1.15 2.0	ectively (T a	ble 4)	7 2.00) 101	
Proximal colon (n=96,307, event=171)					Broad-spectrum	n=54,737; event=159	1.03	0.78 – 1.35	0.852						
Nonuse n=	=38,080; event=45	Ref	-	-	Narrow-spectrum	n=3,527; event=4	0.49	0.18 - 1.33	0.163		•				
Any antibiotic use n=	58,227; event=126	1.63	1.15 – 2.32	0.006	Oral vs intravenous antib	iotics	1		1	- Antibiotics were associated with reduced cancer risk in rectum but increased risk in					
					Nonuse	n=38,126; event=91	Ref	-	-						
Distal colon (n=96,390, event=254)					Oral	N=34,597; event=85	0.94	0.70 - 1.27	0.706	nroximal colon					
Nonuse n=	Nonuse n=38,126; event=91		-	-	Intravenous	N=3,466; event=8	0.85	0.41 - 1.76	0.664	- This phenomenon varied with respect to antibiotic class and spectrum					
Any antibiotic use n=	58,264; event=163	0.99	0.76 – 1.30	0.965	Oral + intravenous	N=20,201; event=70	1.12	0.80 - 1.58	0.513	 Further studies are needed to discern the interaction of antibiotics and topica microbiota on CRC development 					
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	All	Antibiotic us	sers	Antibiotic non-users		No.of patients and events	aHR	95% CI	P-value		No. of patients and events	aHR*	95% CI	p-value		
	(n=97,162)	(n=58,704	L)	(n=38,458)	Rectum (n=96,737, even	t=601)										
Age at index colonoscopy	71.4 (65.1 – 77.8)	72.7 (66.1 – 7	78.9)	69.5 (64.0 – 75.8)	Anti anorohic vs anti aor	obic activity			Rectum (n=96,737, event=601)							
(years)					Anti-allerobic vs anti-aer	n=28 222; overt=287	Dof	1								
Male sex (n, %)	50841 (52.3%)	30625 (52.2	2%)		Nonuse	n=38,322; event=287	Rei	-	-	Nonuse	n=38,372; event=287	Ref	-	-		
History of colonic polyps (n,	29663 (30.5%)	19666 (27.2	2%)	9997 (26.0%)		n=50,381; event=271	0.64	0.53 - 0.76	< 0.001	< 2 weeks	n=21,587; event=127	0.73	0.59 – 0.91	0.004		
%) Polynectomy at index	16087 (16.6%)	10027 (17.1%)		6060 (15.8%)	Anti-aerobic	n=8,034; event=43	0.017									
colonoccony (n. %)	10007 (10.076)				Broad vs harrow spectru		Def		1	\geq 2 weeks	0.48 - 0.71	< 0.001				
Smoking $(n, \%)$	3637 (3.7%)	3332 (5 79	()	305 (0.8%)	Nonuse	n=38,322; event=287	Ret	-	-	Proximal colon (n=9	6.307. event=171)		I			
Alcohol (n. %)	495 (0.5%)	389 (0.7%	5)	106 (0.3%)	Broad-spectrum	n=54,872; event=294	0.63	0.53 - 0.75	< 0.001		· · · · · · · · · · · · · · · · · · ·					
DM (n %)	11442 (11.8%)	10533 (17 9	9%)	909 (9.1%)	Narrow-spectrum	n=3,543; event=20	0.77	0.49 – 1.22	0.277	Nonuse	n=38,080; event=45	Ref	-	-		
Hypertension (n. %)	23512 (24.2%)	17468 (29.8	8%)	6044 (15 7%)	Oral vs intravenous antib	<u>I vs intravenous antibiotics</u>					n-21 509: overt-49	1 72	1 15 - 2 60	0 009		
Dyslipidemia (n. %)	7290 (7.5%)	5112 (8.79	(a)	2178 (5.7%)	Nonuse	n=38,322; event=287	Ref	-	-	< 2 weeks	n=21,505; event=49	1.75	1.15 - 2.80	0.008		
AF (n. %)	5029 (5.2%)	4098 (7.0%	<u>(</u>)	931 (2.4%)	Oral	n=34,690; event=178	0.65	0.54 – 0.78	< 0.001	\geq 2 weeks	n=36,718; event=77	1.57	1.07 – 2.30	0.021		
IHD (n, %)	11141 (11.5%)	8394 (14.3	<u>~,</u> %)	2747 (7.1%)	Intravenous	n=3,481; event=23	0.77	0.50 - 1.18	0.237							
CHF (n, %)	5737 (5.9%)	5045 (8.6%	%)	692 (1.8%)	Oral + intravenous	n=20,244; event=113	0.60	0.47 – 0.76	< 0.001	Distal colon (n=96,3	90, event=254)					
Stroke (n, %)	6541 (6.7%)	5066 (8.6%	%)	1475 (3.8%)	Proximal colon (n=96,307	7, event=171)		1		Nonuse	n=38,126; event=91	Ref	-	-		
CRF (n, %)	2986 (3.1%)	2664 (4.5%	%)	322 (0.8%)	Anti-anaerobic vs anti-ae	erobic activity										
Cirrhosis (n, %)	696 (0.7%)	593 (1.0%	5)	103 (0.3%)	Nonuse	n=38,080; event=45	Ref	-	-	< 2 weeks	n=21,512; event=52	0.92	0.65 - 1.30	0.634		
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Parkinsonism (n, %)	726 (0.7%)	585 (1.0%	5)	141 (0.4%)	Anti-aerohic	n=8 005: event=14	1 33	0 73 – 2 43	0 354		n=30,732, cvcnt=111	1.04	0.70 1.40	0.700		
Aspirin (n, %)	22004 (22.6%)	15864 (27.0)%)	6140 (16.0%)	Broad vs parrow spectru	m activity	1.55	0.75 2.45	0.554							
NSAIDs (n, %)	8000 (8.2%)	5649 (9.6%	%)	2351 (6.1%)	Broad vs harrow spectru		Def		1	_						
COX-2 inhibitors (n,%)	108 (0.1%)	71 (0.1%))	37 (0.1%)	Nonuse	n=38,080; event=45	Ret	-	-	Results						
Statins (n,%)	17651 (18.2%)	11629 (19.8	3%)	6022 (15.7%)	Broad-spectrum	n=54,695; event=11/	1.60	1.13 - 2.29	0.009	itteatte						
Annual center endoscopy	2892	2892		2887	Narrow-spectrumn=3,532; event=92.08			1.02 – 4.27	0.045	- 97,162 (male: 50,841 [52.3%]); median age at index colonoscopy: 71.4 ye						
volume	(2045 – 3316)	(2054 – 331	(2054 – 3316) (2033 – 3291)		Oral vs intravenous antib	<u>piotics</u>	1	1	1	(IQR:65.1–77.8) (Table 1)						
Annual center polypectomy	24.6%	24.6%		24.7%	Nonuse	n=38,080; event=45	Ref	-	-	- Median duratior	n of antibiotic use: 15 days (IC	R:7–31)				
rate*	(21.7% - 28.2%) (21.7% - 28.0%) (21		(21.6% - 28.4%)	Oral	n=34,580; event=68	1.53	1.05 – 2.24	0.028	- Pre-colonoscopy antibiotics were associated with lower rectal cancer							
					Intravenous	n=3,470; event=12	2.61	1.37– 4.97	0.004	(aHR:0.64;95%	CI:0.54–0.76) but high	ner proxi	imal colon car	ncer risk		
					Oral + intravenous	n=20,177; event=46	1.65	1.07 – 2.56	0.024	(aHR:1.62;95%)	CI:1.14–2.30); while there w	as no sigr	nificant associatior	n between		
Table 2. Association betw	veen antibiotics and C	RC after index	colonoso	copy negative for CRC	Distal colon (n=96,390, e	event=254)				antibiotics and distal colon cancer (aHR:0.99;95% CI:0.76–1.30) (Table 2)						
Nur	nber of patients and	aHR*	95% CI	p-value	Anti-anaerobic vs anti-ae	erobic activity		- Differential effects of antibiotics on CRC according to their (1) anti-anaerobic vs								
events					Nonuse	n=38,126; event=91	Ref	-	-	anti-aerobic act	ivity, (2) broad-spectrum vs n	arrow spec	ctrum activity, and	(3) oral vs		
Rectum (n=96,737, event=601)					Anti-anaerobic	n=50,252; event=142	0.99	0.75 – 1.31	0.944	intravenous vs l	both route (Table 3)			/		
Nonuse n=	-38,372; event=287	Ref	-	-	Anti-aerobic	n=8,012; event=21	1.02	0.63 - 1.64	0.944	- The aHR of rec	tal cancer with antibiotic use <	<2 weeks a	and ≥2 weeks was	0.73 (95%		
Any antibiotic use n=	58,480; event=314	0.64 0.5	54 - 0.76	< 0.001	Broad vs narrow spectru	m activity		1		CI:0.59-0.91	and $0.58 (95\% \text{ CI:} 0.48-0.71)$), respection (0) and (1)		mai colon		
					Nonuse	n=38,126; event=91	Ref	-	-		was $1.73 (95\% \text{ Cl.}1.15-2.0)$	otivoly (Ta l	(95% CI.1.07)	-2.30) 101		
Proximal colon (n=96,307, event=171)				Broad-spectrum	n=54,737; event=159	1.03	0.78 – 1.35	0.852		2 weeks and 22 weeks, respe						
Nonuse na	=38,080; event=45	Ref	-	-	Narrow-spectrum	n=3,527; event=4	0.49	0.18 - 1.33	0.163		•					
Any antibiotic use n=	y antibiotic use n=58,227; event=126 1.63 1.15 – 2.32 0.006		0.006	Oral vs intravenous antib	<u>biotics</u>			1	Conclusion							
				Nonuse	n=38,126; event=91	Ref	-	-	- Antibiotics were associated with reduced cancer risk in rectum but increased risk in							
Distal colon (n=96,390, event=254) Nonuse n=38,126: event=01 Pof					Oral	N=34,597; event=85	0.94	0.70 - 1.27	0.706	proximal colon						
			-		Intravenous	N=3,466; event=8	0.85	0.41 - 1.76	0.664	- This phenome	non varied with respect to ant	ibiotic clas	s and spectrum			
Any antibiotic use n=	≥38,204; event=163	0.99 0.7	ν ο - 1.30	0.965	Oral + intravenous	N=20,201; event=70	1.12	0.80 - 1.58	0.513	- Further studie	s are needed to discern the	interaction	of antibiotics and	topical gut		
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KS Cheung¹, EW Chan², WK Seto¹, ICK Wong,^{1, 3} WK Leung¹

 Table 3. Association between nature of antibiotics and CRC according to cancer subsite

Table 4. Assciation between CRC and duration of antibiotic use

