Frequent antibiotic prescription and risk of encephalopathy related hospitalisation among people living with dementia: a population-based cohort study

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INTRODUCTION

Neurodegenerative and causes behavioral and psychiatric symptoms

- Prone to neurotoxicity [1]
- Higher risk of developing encephalopathy [1]
- Hospitalization-related delirium risk is high

Antibiotics – Most commonly prescribed drug, has worrying side effects

- Known side effects include neurotoxicity, delirium and encephalopathy [3]
- Unclear risk in dementia special population
- Study in England showed frequent antibiotics prescription can harm patients and increase risk of hospitalization [2]

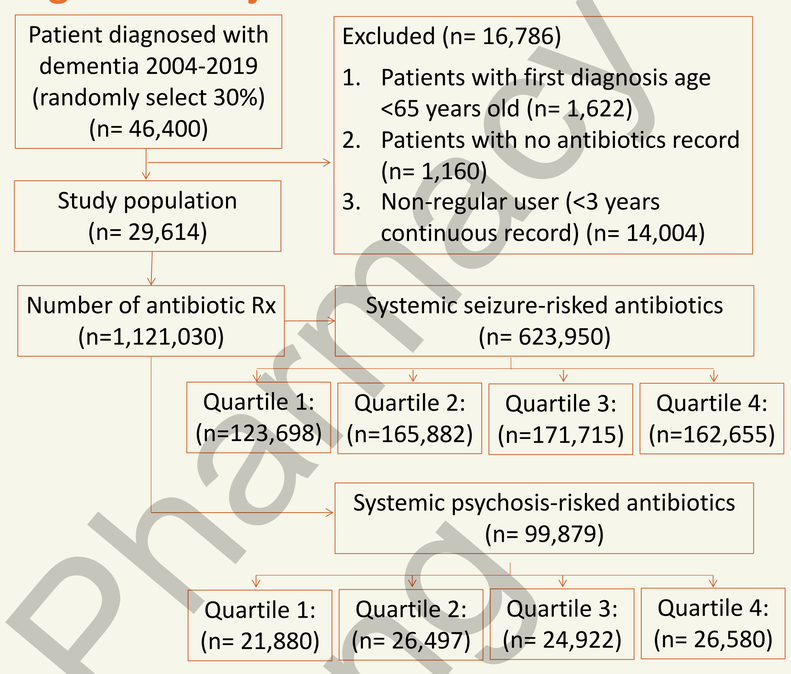
How does antibiotics prescription affect encephalopathy

- Encephalopathy types (type 1: seizure vs type 2: psychosis) [3]
- Current literature suggest seizure-high risk antibiotics include penicillin, cephalosporin, tetracyclines and aminoglycosides, while psychosis-risked antibiotics include macrolides, quinolones, sulphonamides, tetracyclines and aminoglycosides [3]

OBJECTIVES

- To evaluate the current antibiotic prescribing patterns in Hong Kong among people living with dementia
- To evaluate the association between frequency of high-risk antibiotic prescriptions and the risk of hospitalization due to seizure (type 1 encephalopathy) among people living with dementia
- To evaluate the association between frequency of high-risk antibiotic prescriptions and the risk of hospitalization due to psychosis (type 2 encephalopathy) among people living with dementia

Figure 1: Subject selection



METHODOLOGY

Patients with dementia diagnosis 2004-2019 in CDARS is identified, 30% of which is randomly selected in this study (Figure 1)

1. First diagnosis age ≥65years old
2. Patients with at least one antibiotic prescription record
3. Regular user of healthcare services

Antibiotic prescriptions by systemic routes are grouped by antibiotic class

- High risk classes are selected for each analysis arm (Seizure vs Psychosis)[3]

Frequency count of exposure is total number of antibiotic prescriptions received 182 days before index antibiotic (figure 2)

Outcome follow-up period will be the 30 days after the index antibiotic (figure 2)

Quartiles are divided by the frequency of exposure into 4 subgroups with increasing frequency

Propensity score was estimated by logistic regression, include age, sex, index year, Charlson Comorbidity Index Score (CCS) and prior encephalopathy history (table 1)

Risk is calculated with negative binomial regression model expressed in IRR (adjust by propensity score) (figure 3)

Figure 2: Exposure frequency count

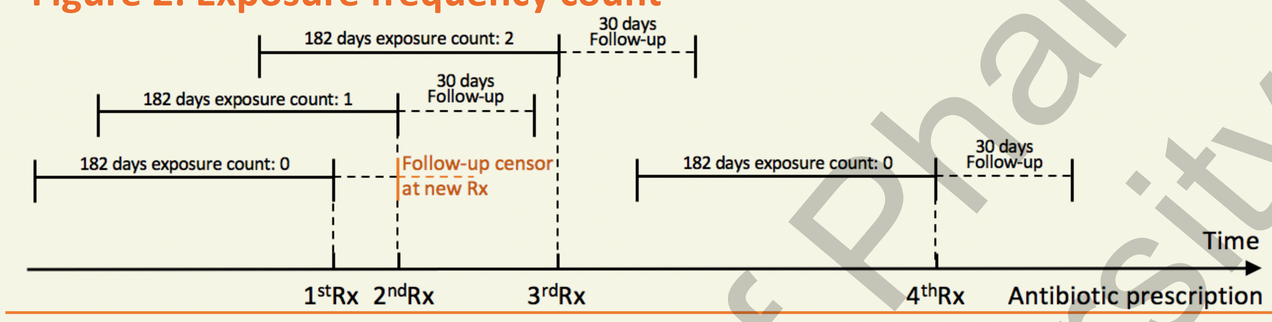


Table 1: Quartiles baseline characteristics

Seizure outcome analysis:

	Whole cohort	Quartile of prior antibiotic use (Frequency of script) Lowest (0-2)	Low (3-8)	Medium (9-19)	Highest (20+)
Number of scripts	623950	123698	165882	171715	162655
Age (mean)	86.2	86.1	86.5	86.5	85.8
First Dx age (mean)	83.6	83.1	83.2	83.1	82.8
Women (%)	254132 (40.7)	42956 (34.7)	62354 (37.6)	70699 (41.2)	78123 (48.0)
CCS					
Lowest(0)(%)	86231 (13.8)	20701 (16.7)	24650 (14.9)	23031 (13.4)	17849 (11.0)
Low(1-2) (%)	290838 (46.6)	59550 (48.1)	78109 (47.1)	79021 (46.0)	74158 (45.6)
Mid(3-4) (%)	167174 (26.8)	30117 (24.3)	42951 (25.9)	47028 (27.4)	47078 (28.9)
High(5-6) (%)	50958 (8.2)	8500 (6.9)	12674 (7.6)	14165 (8.2)	15619 (9.6)
Highest(7+)(%)	28749 (4.6)	4830 (3.9)	7498 (4.5)	8470 (4.9)	7951 (4.9)
Seizure history	12338 (19.8)	1938 (15.7)	2949 (17.8)	3466 (20.2)	3985 (24.5)

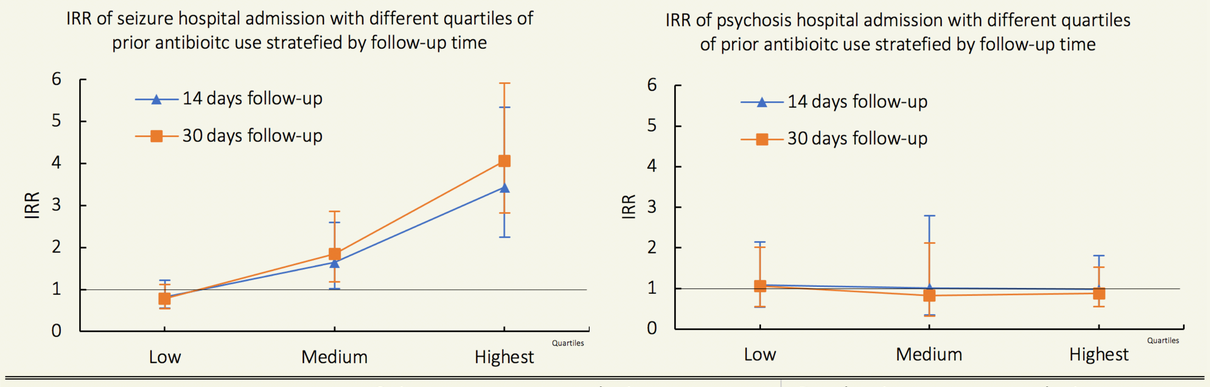
Psychosis outcome analysis:

	Whole cohort	Quartile of prior antibiotic use (Frequency of script) Lowest (0)	Low (1-2)	Medium (3-6)	Highest (7+)
Number of scripts	99879	21880	26497	24922	26580
Age (mean)	85.9	86.0	86.1	86.0	85.4
First Dx age (mean)	83.6	82.8	82.8	82.7	82.3
Women (%)	57751(57.8)	13411(61.3)	15831(59.7)	14257(57.2)	14252(53.6)
CCS					
Lowest(0) (%)	14066 (14.1)	3374 (15.4)	3891 (14.7)	3507 (14.1)	3294 (12.4)
Low(1-2) (%)	46342 (46.4)	10336 (47.2)	12498 (47.2)	11547 (46.3)	11961 (45.0)
Mid(3-4) (%)	27076 (27.1)	5631 (25.7)	6976 (26.3)	6742 (27.1)	7727 (29.1)
High(5-6)(%)	7800 (7.8)	1632 (7.5)	2001 (7.6)	2011 (8.1)	2129 (8.0)
Highest(7+) (%)	4595 (4.6)	907 (4.1)	1131 (4.3)	1115 (4.5)	1469 (5.5)
Psychosis history	48357 (48.4)	10171 (46.5)	12785 (48.3)	12252 (49.2)	13149 (49.5)

RESULTS

- Risk of seizure increase sharply along with quartiles of higher exposure frequencies, achieved significance in medium quartile and was even stronger for highest quartile. Slightly more significant association for 30 days follow-up period than in 14 days. Risk of seizure was over 4 times as likely compared to lowest quartile (IRR 4.06 [95%CI 2.82- 5.91]).
- No association was found for psychosis, in primary analysis and all sensitivity analysis. Seizure IRR remained significant in all sensitivity analysis in highest quartile comparison.
- Younger patient subgroup (age 65-84) displayed stronger association between highest antibiotic prescriptions frequency and seizure risk. Older subgroup (age≥85) showed less variations but consistently significant. (table 2)

Figure 3: IRR of encephalopathy between quartiles



	Seizure outcome analysis		Psychosis outcome analysis	
Quartile of prior antibiotic use	14days follow up IRR (95% CI)	30days follow up IRR (95% CI)	14days follow up IRR (95% CI)	30days follow up IRR (95% CI)
Lowest	Reference	Reference	Reference	Reference
Low	0.82 (0.55-1.22)	0.78 (0.54-1.12)	1.09 (0.54-2.14)	1.06 (0.55-2.02)
Medium	1.64 (1.02-2.60)	1.84 (1.18-2.86)	1.01 (0.35-2.79)	0.83 (0.32-2.12)
Highest	3.43 (2.24-5.34)	4.06 (2.82-5.91)	0.98 (0.55-1.81)	0.88 (0.55-1.52)

Table 2: Sensitivity analysis IRRs

	Quartile of prior antibiotic use				
		Seizure outcome analysis		Psychosis outcome analysis	
Sub-group	Lowest	Medium IRR (95%CI)	Highest IRR (95%CI)	Medium IRR (95%CI)	Highest IRR (95%CI)
Age < 85 years old	Ref	1.56 (0.85-2.83)	5.00 (2.91-8.79)	1.67 (0.48-5.55)	1.33 (0.66-2.81)
Age ≥ 85 years old	Ref	2.22 (1.28-3.82)	2.41 (1.51-3.93)	0.32 (0.04-2.17)	0.53 (0.24-1.68)
No COPD/ Cancer	Ref	1.36 (0.76-2.41)	3.90 (2.42-6.38)	0.81 (0.24-2.60)	1.16 (0.56-2.52)
365 days exposure count	Ref	1.50 (0.87-2.56)	4.48 (3.08-7.22)	0.77 (0.20-2.80)	0.66 (0.37-1.15)
All-cause hospitalisation	Ref	0.91 (0.85-0.97)#	1.40 (1.35-1.46)#	--	--

#: IRR of all-cause hospitalisation as outcome

DISCUSSION

- Strong dose-response was found between risk of seizure and frequency of antibiotic prescriptions the patient received. Depending on age and prior antibiotic received, patients with dementia can experience up to 4-5 times as likely risk of seizure compared to those with least antibiotics received.
- For younger patients, caution should be put on limiting the maximum frequency of antibiotics a patient should be prescribed. Whereas for older patients, due to higher sensitivity to seizure risk, should be cautious for any frequency of antibiotic prescription

CONCLUSION

- Encephalopathy is a serious health concern, especially in patients with impaired brain function, like those with dementia. Benefit of some antibiotic indications might not be justified with such risk.
- Seizure might lead to further clinical complications and jeopardize patients' morbidity and quality of life
- Future research direction on long term association, possible mechanism of association and mode of association

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