Are shorter antibiotic courses associated with increased mortality or readmission risk in acute/general medicine inpatients?

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Background

- In England, acute/general medicine inpatients are largest consumers of non-prophylactic antibiotics in hospitals[1], and hospital prescribing accounts for >65% of broad-spectrum antibiotic use[2]
- Broad-spectrum antibiotics have greatest potential to drive future resistance, and doctors need to balance risks of under-treating infections against risks of future antibiotic-resistance
- Clinicians' are often reluctant to modify prescribing decisions made by others[3], which may lead to overuse of antibiotics
- **Aim: to determine whether there was any evidence of harm associated with reduced antibiotic exposure in hospital**

Challenge

- "Less sick" individuals likely have lower antibiotic exposure
- Can therefore predict what we expect to find depending on how much confounding we can control for (Table 1)

Table 1	Unknown 'true' impact of reduced antibiotic exposure	
This observational analysis	**Non-inferiority in terms of mortality with less antibiotic exposure**	**Inferiority in terms of mortality with less antibiotic exposure (reduced antibiotic use leads to harm)**
Relatively successfully controlled for confounding (provide approximately unbiased inference)	No observational association between antibiotic use and outcome	Shorter antibiotics appear to be associated with harm
Not successfully controlled for confounding (residual bias from less sick individuals receiving fewer antibiotics and having better outcomes)	Shorter antibiotics appear to be associated with residual benefit	No observational association between antibiotic use and outcome

- In observational studies, not observing harm (grey/white cells) from reduced antibiotic use is *necessary* to conclude no harm, though not *sufficient* (due to concerns about residual confounding)

Methods

- Observational analysis of anonymised electronic health record data from adult (≥16 years) inpatients admitted to acute/general medicine between 01/01/2010-31/12/2015 in UHB NHS Foundation Trust
- Used Cox models to estimate the time-varying effect of patient-level antibiotic exposure on 30-day mortality and the cause-specific hazard of 30-day readmission following discharge
- Exposures: ever received antibiotics, broad-spectrum antibiotics, or IV antibiotics; defined-daily-dose (DDD); days-of-therapy (DOT), broad-spectrum DOT, IV-DOT, and length-of-therapy (LOT)
- Models adjusted for age, sex, ethnicity, index of multiple deprivation score, immunosuppression, Charlson comorbidity score, admission day-of-week, day-of-year, calendar year, admission method, previous admissions in past year, and any prior complex admission

Results

- 4,867 (3.9%) deaths within 30 days of 125,783 inpatient admissions, and 31,560 (25.1%) ever received antibiotics
- 10,386 (8.6%) readmissions within 30 days of 120,136 discharges, and 27,990 (23.3%) ever received antibiotics

Table 2: Admission characteristics in acute/general medicine

Characteristics	Exposure	N=125,783 admissions
Age	Median (IQR)	61 (44-76)
Sex	Female	67,263 (53.5%)
Ethnicity	White	92,092 (73.2%)
	Unknown	10,164 (8.1%)
	Black	4,440 (3.5%)
	Asian	14,840 (11.8%)
	Other	4,247 (3.4%)
Index of multiple deprivation score	Median (IQR) 100 pt scale	30.7 (18.6-48.1)
Charlson comorbidity score	Median (IQR)	0 (0-5)
Immunosuppression	Yes	8,602 (6.8%)
Admission day-of-week	Weekday	104,552 (83.1%)
Previous admissions in past year	Median (IQR)	0 (0-1)
Any prior complex admission	Yes	18,926 (15.1%)

Table 3: Impact of antibiotic use on 30-day mortality/readmission

Exposure		30-day mortality: 3,778,833 days at risk				30-day readmission: 3,491,741 days at risk	
		N (col %) or median (IQR)	N dead (row %) or median(IQR)	Univariable HR (95% CI)	Multivariable HR (95% CI)	Univariable HR (95% CI)	Multivariable HR (95% CI)
Ever on any abx	Yes vs no	874,770 (23.1%)	3,281 (0.4%)	7.02 (6.61-7.45)	2.89 (2.71-3.08)	1.81 (1.74-1.88)	1.26 (1.21-1.32)
Ever on broad-spectrum abx	Yes vs no	506,239 (13.4%)	2,827 (0.6%)	9.17 (8.66-9.71)	4.31 (4.06-4.59)	1.81 (1.73-1.90)	1.29 (1.23-1.36)
Ever on IV abx	Yes vs no	476,441 (12.6%)	2,863 (0.6%)	10.07 (9.51-10.67)	4.62 (4.35-4.91)	1.76 (1.67-1.84)	1.26 (1.19-1.32)
Defined-daily-dose (DDD)*	Per additional 10 DDD	9.0 (5.0-15.9)	6.0 (2.6-12.1)	1.10 (1.06-1.15)	1.09 (1.05-1.14)	1.02 (0.99-1.05)	0.99 (0.96-1.03)
Days-of-Therapy (DOT)*	Per additional DOT	8 (6-14)	7 (4-12)	1.05 (1.04-1.05)	1.04 (1.04-1.05)	1.01 (1.00-1.01)	1.00 (1.00-1.01)
Broad-spectrum DOT*	Per additional DOT	7 (4-10)	5 (2-9)	1.06 (1.05-1.07)	1.06 (1.05-1.07)	1.01 (1.00-1.02)	1.00 (0.99-1.01)
IV-DOT*	Per additional DOT	5 (2-8)	5 (3-9)	1.11 (1.11-1.12)	1.11 (1.10-1.12)	1.01 (1.00-1.02)	1.00 (0.99-1.01)
Length-of-Therapy (LOT)*	Per additional LOT	7 (5-10)	6 (3-9)	1.06 (1.05-1.06)	1.06 (1.05-1.06)	1.01 (1.01-1.02)	1.00 (1.00-1.01)

* Models for cumulative exposures were also adjusted for ever vs never on antibiotics

- **Conclusion: No evidence reduced antibiotic use associated with increased mortality or readmission risk (not in red cell, Table 1)**
- Adjusted estimates may still be subject to residual confounding (from infection severity, comorbidity)
- Next: will investigate impact of adjusting haematology and biochemistry test results (reflecting illness severity), and degree of unmeasured confounding required to miss harms from shorter antibiotic courses.

References: [1] HPA. English national point prevalence survey on healthcare-associated infections and antimicrobial use, 2011, 2012. [2] PHE. ESPAUR Report 2014. [3] Charani E, *et al.* Clin Infect Dis 2013; 57(2):188-96
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