Incidence of antibiotic-associated diarrhea and *Clostridium difficile* infection in Europe

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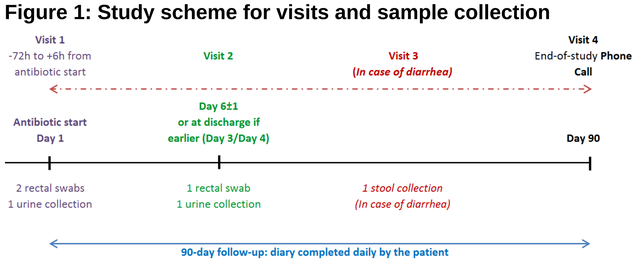
BACKGROUND:

- Antibiotic-associated diarrhea (AAD) and *Clostridium difficile* infection (CDI) are frequent complications of broad-spectrum antibiotic treatment
- Antibiotic-specific incidence rates in European countries are not well documented
- We assessed the incidence and predictive value of biomarkers of AAD and CDI in the "AssessmeNT of the Incidence of *Clostridium difficile* Infections in hospitalized Patients on Antibiotic TrEatment" (ANTICIPATE study)
- The aim was to collect epidemiological data and identify bottlenecks to optimally design a trial of DAV132, a product designed for prevention of antibiotic-induced CDI

METHODS:

- Multicenter prospective observational cohort study in 34 hospitals in France, Germany, Greece, the Netherlands, Romania, and Spain
- Diarrhea was defined as three or more unformed stools per 24 hours (Bristol Stool Chart type 5-7)
- CDI was diagnosed according to ESCMID diagnostic guidelines

Figure 1: Study scheme for visits and sample collection



Eligibility criteria

Inclusion criteria
- Age ≥ 50 years
- Being hospitalized
- Systemic treatment >= 5 days with
  - 3rd or 4th generation cephalosporin
  - Fluoroquinolone
  - penicillin + beta-lactamase inhibitor
  - clindamycin
  - carbapenem

Exclusion criteria
- On treatment with above classes >6 hours
- (Anticipated) ICU admission
- (Treatment for) suspected or diagnosed CDI, or diarrhea at inclusion
- Previously included subject
- Treatment with probiotics to prevent CDI
- Stoma (jejunostomy, ileostomy, or colostomy)
- Social or logistical condition which interferes with conduct of study
- Subject of legal age under legal protection
- Subject deprived of liberty by judicial or administrative decision

Statistics:

- Incidences of AAD and CDI within 28 and 90 days after initiating antibiotic treatment were computed using the Kaplan-Meier estimator
- Analyses of predictive factors for CDI using Cox regression
- Known missing stool tests were assumed negative

RESULTS:

Between Sep 2016 and Oct 2017, 1007 evaluable patients were enrolled. A total of 86 subjects died and 86 were withdrawn or lost to follow-up.

Table 1: Baseline characteristics

Variable	N=1,007
Age	70 (62 - 79)
Male gender	592 (59%)
Charlson comorbidity index	5 (4 - 7)
Myocardial infarction	83 (8%)
Congestive heart failure	144 (14%)
Peripheral vascular disease	153 (15%)
Cerebrovascular disease	85 (8%)
COPD	160 (16%)
Diabetes mellitus	281 (28%)
Chronic kidney disease	132 (13%)
Hematological malignancy	129 (13%)
Solid tumor	223 (22%)
Liver disease	92 (9%)
History of CDI	14 / 921 (2%)
Started on antibiotic monotherapy	687 (68%)
Started on antibiotic combination therapy	320 (32%)

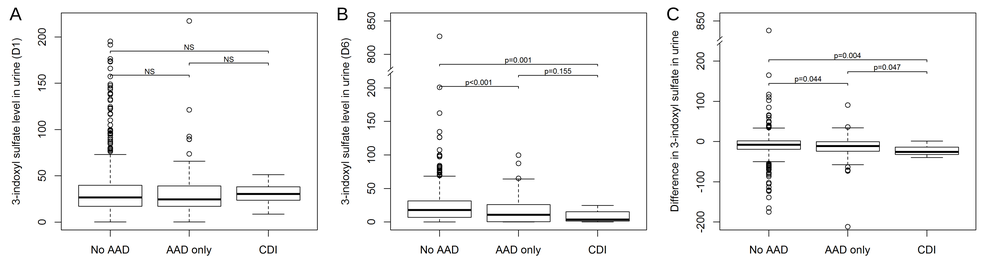
Median (IQR) for continuous and N (%) for categorical data

AAD / CDI

In 134 subjects a total of 178 AAD episodes occurred. Stool samples were collected in 127 (71%) and yielded 17 CDI episodes in 15 unique subjects.

Figure 2: Urine 3-indoxyl sulfate levels in non-AAD, AAD-only, and CDI patients:

A) baseline, B) Day 6 +/- 1, and C) change from Day 1 to 6. Statistical testing with Kruskal-Wallis rank sum test followed by Mann-Whitney test if p-value <0.05. NS: Not significant on Kruskal-Wallis test. The table shows the corresponding median and IQR.



	A			B			C		
	No AAD	AAD only	CDI	No AAD	AAD only	CDI	No AAD	AAD only	CDI
Median	26.8	24.5	30.5	17.9	10.7	3.7	-8.1	-10.9	-25.5
25th pct	17.0	17.1	23.6	7.0	0.6	1.6	-19.3	-23.9	-32.0
75th pct	39.8	39.0	38.2	31.6	26.0	12.8	1.9	-0.3	-14.2

CONCLUSIONS:

ANTICIPATE provides epidemiological data on AAD and CDI in at-risk patients and facilitates enrichment of study target populations and designs for upcoming randomized controlled trials on prevention of AAD and CDI

- CDI incidence within 28 and 90 days was 0.9% and 1.6% in this study population
- Carbapenem use and colonisation with *C. difficile* were associated with increased CDI incidence
- Median time to CDI in colonised compared to non-colonised patients is substantially shorter (2 vs. 30 days)
- A decrease in urine 3-indoxyl sulfate level at Day 6, but not the baseline level, is associated with AAD and CDI
- 75% of CDI cases occurred within 38 days so a shorter follow-up may be considered
- Collection of stool samples after discharge was challenging, potentially leading to underestimation of CDI incidence
- The analyses on microbiota (16S) and the full analyses of risk factors for CDI are still ongoing

Table 2: Incidence of first episode of AAD and CDI

		28 days follow-up period (after initiating antibiotic treatment)					*90 days follow-up period (after initiating antibiotic treatment)*					
Population	**N**	**#AAD**	**AAD incidence (CI)**	**#CDI**	**CDI incidence (CI)**	**HR for CDI (CI)**	**#AAD**	**AAD incidence (CI)**	**#CDI**	**CDI incidence (CI)**	**HR for CDI (CI)**	**Time to CDI***
Total population	1007	101	10.4% (8.7-12.5)	9	**0.9% (0.5-1.8)**	-	134	13.8% (11.7-16.1)	15	**1.6% (1.0-2.6)**	-	18 (4-38)
Antibiotic class at baseline §												
Penicillin + bl inhibitor	409	45	11.4% (8.7-15.0)	4	1.0% (0.4-2.7)	1.18 (0.32 - 4.40) ‡	51	12.8% (9.9-16.5)	5	1.3% (0.5-3.1)	0.74 (0.25 - 2.16) ‡	15 (3-18)
3rd/4th gen cephalosporin	391	28	7.8% (5.4-11.0)	3	0.8% (0.3-2.6)	0.78 (0.20 - 3.13) ‡	44	12.1% (9.1-16.0)	6	1.7% (0.8-3.7)	1.05 (0.37 - 2.94) ‡	24 (9-33)
Fluoroquinolone	181	18	10.4% (6.7-16.0)	1	0.6% (0.1-4.1)	0.57 (0.07 - 4.53) ‡	24	14.0% (9.6-20.1)	2	1.2% (0.3-4.7)	0.70 (0.16 - 3.09) ‡	32 (22-42)
Carbapenem	64	15	24.1% (15.4-36.5)	2	3.2% (0.8-12.2)	4.19 (0.87 - 20.15) ‡	20	32.2% (22.2-45.2)	4	6.5% (2.5-16.2)	**5.31 (1.69 - 16.68)** ‡	23 (10-45)
Clindamycin	29	2	7.6% (2.0-26.4)	0	-	-	3	11.4% (3.9-30.8)	0	-	-	-
Medical history												
History of CDI	14	2	15.4% (4.6-45.0)	0	-	-	2	15.4% (4.6-45.0)	0	-	-	-
No history of CDI	907	88	10.1% (8.3-12.3)	8	0.9% (0.5-1.8)	-	120	13.7% (11.6-16.2)	14	1.6% (1.0-2.7)	-	18 (4-41)
Biomarkers at baseline												
C. difficile carriage	35	7	20.0% (10.2-36.9)	4	11.4% (4.6-27.0)	**22.67 (6.09 - 84.44)**	7	20.0% (10.2-36.9)	4	11.4% (4.6-27.0)	**10.31 (3.28 - 32.39)**	2 (1-3)
No *C. difficile* carriage	947	92	10.1% (8.3-12.3)	5	0.6% (0.2-1.3)	-	124	13.6% (11.5-16.0)	11	1.2% (0.7-2.2)	-	30 (16-44)
High 3-indoxyl sulfate	466	48	10.7% (8.2-14.0)	6	1.3% (0.6-3.0)	2.06 (0.52 - 8.24)	61	13.6% (10.7-17.1)	9	2.0% (1.1-3.9)	1.55 (0.55 - 4.36)	12 (3-30)
Low 3-indoxyl sulfate	472	48	10.5% (8.0-13.7)	3	0.7% (0.2-2.0)	-	67	14.6% (11.7-18.2)	6	1.3% (0.6-3.0)	-	26 (16-48)

** median (IQR) in days. § Subjects can be included in more than one antibiotic subgroup. ‡ compared to patients not receiving this antibiotic class at baseline. CI: 95% confidence interval. HR: Hazard Ratio.*

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