SUPPLEMENTARY TABLES

Supplementary table 1 Variables included in multivariable analysis and calculated Schoenfeld residuals for the Cox regression model

Variable	Chi square	Degrees of freedom	P value
Cephalosporins	0.35	1	0.56
Penicillin-BLIs	0.76	1	0.38
Metronidazole	0.46	1	0.50
Penicillins	0.94	1	0.33
Macrolides	0.07	1	0.79
Fluoroquinolones	0.29	1	0.59
Adalimumab	0	1	0.99
Crohn's	1.34	1	0.25
Previous anti-TNF	0.51	1	0.47
Hospitalizations	0.14	1	0.71
Surgeries	0.34	1	0.56
Albumin (per 1 g/dL)	0.03	1	0.86
CRP (per 1 mg/dL)	3.84	1	0.05
Corticosteroids	0.65	1	0.42
Methotrexate	0.02	1	0.89
Thiopurines	0.06	1	0.81
Global	13.3	16	0.65

Supplementary table 2 Comparison of Proportions and follow up times for patients treated and untreated with various antibiotic classes during follow up and patients with and without antidrug antibodies. For each variable, comparison for each time period was performed using the Mann-Whitney U test. All comparisons showed significant differences with p-values<0.05.

Antibiotic class	**Number and percentage of treated**	**Time to first ADA measure in treated**	**Time to first ADA measure in untreated**	**Time to last ADA measure in treated**	**Time to last ADA measure in untreated**
Cephalosporins	882 (45.3%)	854 (1,508)	421 (847)	948 (1,481)	493 (875)
Penicillin-BLIs	934 (48.0%)	941 (1,540)	388 (766)	1,024 (1,494)	456 (802)
Penicillins	985 (50.6%)	911 (1,467)	365 (765)	990 (1,435)	447 (792)
Metronidazole	1,188 (61.0%)	762 (1,425)	374 (774)	827 (1,391)	426 (828)
Macrolides	131 (6.7%)	831 (1,202)	559 (1,124)	880 (1,256)	638 (1,158)
Fluoroquinolones	320 (16.4%)	1,960 (1,678)	449 (851)	2,009 (1,673)	511 (868)
	Number and percentage of positive	**Time to first ADA measure in positive**	**Time to first ADA measure in negative**	**Time to last ADA measure in positive**	**Time to last ADA measure in negative**
Antidrug antibodies	368 (18.9%)	385 (844)	645 (1,252)	402 (853)	720 (1,222)

ADA, antidrug antibodies

Supplementary Table 3 Multivariable adjusted hazard ratios for ADA development during anti-TNF therapy. Data is shown for Cox proportional hazards models in which antibiotic classes were incorporated as time dependent covariates. Interaction terms for combination of pairs of cephalosporins, penicillins with BLIs, macrolides and fluroquinolones were added to explore possible synergism or antogonism.

Variable	aHR (95% CI)
Antibiotic use, 1 year prior	
Cephalosporins	1.59 (1.17-2.15)
Penicillin-BLIs	1.10 (0.80-1.51)
Metronidazole	0.88 (0.70-1.10)
Penicillins	0.79 (0.64-0.99)
Macrolides	0.49 (0.13-1.79)
Fluoroquinolones	0.12 (0.04-0.39)
Interaction terms	
Cephalosporins:Penicillin-BLIs	1.56 (1.01-2.42)
Cephalosporins:Macrolides	0.77 (0.14-4.23)
Cephalosporins:Fluoroquinolones	1.25 (0.35-4.40)
Penicillin-BLIs:Macrolides	0.77 (0.14-4.19)
Penicillin-BLIs:Fluroquinolones	1.66 (0.47-5.90)
Macrolides:Fluoroquinolones	0.00 (0.00-inf)
Secondary effects	
Adalimumab vs infliximab	0.53 (0.43-0.66)
Crohn's vs UC	0.67 (0.51-0.87)
Previous anti-TNF (yes vs no)	1.52 (1.23-1.88)
Hospitalizations (yes vs no)	0.89 (0.79-1.00)
Surgeries (yes vs no)	1.18 (0.90-1.54)
Albumin (per increase of 1 g/dL)	0.94 (0.74-1.18)
CRP (per increase of 1 mg/dL)	1.03 (1.02-1.03)
Corticosteroids (yes vs no)	1.16 (0.90-1.50)
Methotrexate (yes vs no)	0.84 (0.58-1.23)
Thiopurines (yes vs no)	0.66 (0.53-0.82)

aHR, adjusted hazard ratio; CI, confidence interval; CRP, C-reactive protein; BLI, beta lactamase inhibitors

Supplementary Table 4 Multivariable adjusted hazard ratios for ADA development during anti-TNF therapy. Data is shown for Cox proportional hazards models in which antibiotic classes were incorporated as time dependent covariates as either categorical variables defined as any use of specific class during the time period (1 year) in one model or as continuous variables defined as total sum of dispensations of antibiotics from this class during the same period in the second model.

Variable	aHR (95% CI)	
	Categorical	**Continuous**
Antibiotic use, 1 year prior		
Cephalosporins	1.78 (1.40-2.27)	1.36 (1.22-1.51)
Penicillin-BLIs	1.45 (1.14-1.85)	1.23 (1.11-1.35)
Metronidazole	0.85 (0.65-1.13)	0.97 (0.91-1.04)
Penicillins	0.55 (0.41-0.77)	0.75 (0.62-0.91)
Macrolides	0.29 (0.04-2.21)	0.29 (0.04-1.96)
Fluoroquinolones	0.18 (0.06-0.50)	0.31 (0.14-0.66)
Secondary effects		
Adalimumab vs infliximab	0.53 (0.43-0.66)	0.54 (0.43-0.67)
Crohn's vs UC	0.63 (0.48-0.81)	0.62 (0.48-0.80)
Previous anti-TNF (yes vs no)	1.47 (1.19-1.82)	1.51 (1.21-1.85)
Hospitalizations (yes vs no)	0.99 (0.86-1.14)	0.99 (0.90-1.08)
Surgeries (yes vs no)	0.90 (0.62-1.31)	0.98 (0.90-1.07)
Albumin (per increase of 1 g/dL)	0.95 (0.75-1.21)	0.97 (0.77-1.23)
CRP (per increase of 1 mg/dL)	1.03 (1.02-1.03)	1.03 (1.03-1.04)
Corticosteroids (yes vs no)	1.41 (1.02-1.95)	1.38 (0.99-1.90)
Methotrexate (yes vs no)	0.99 (0.65-1.52)	0.98 (0.68-1.49)
Thiopurines (yes vs no)	0.63 (0.50-0.78)	0.62 (0.50-0.78)

aHR, adjusted hazard ratio; CI, confidence interval; CRP, C-reactive protein; BLI, beta lactamase inhibitors

Supplementary Table 5 Multivariable adjusted hazard ratios for ADA development during anti-TNF therapy with assessment of imputed variables (CRP and albumin). Data is shown for Cox proportional hazards models in which antibiotic classes were incorporated as time dependent categorical covariates. Data is presented for the complete cohort (n=1,946) but with a model that does not include CRP, and albumin, or for a partial cohort (n=1,497) of patients that have available information for all variables.

Variable	aHR (95% CI)	
	CRP, albumin excluded	**Partial cohort**
Antibiotic use, 1 year prior		
Cephalosporins	2.12 (1.71-2.62)	1.83 (1.42-2.35)
Penicillin-BLIs	1.44 (1.16-1.79)	1.34 (1.04-1.73)
Metronidazole	0.85 (0.68-1.06)	0.79 (0.61-1.04)
Penicillins	0.78 (0.63-0.97)	0.75 (0.58-0.97)
Macrolides	0.37 (0.16-0.82)	0.35 (0.14-0.85)
Fluoroquinolones	0.24 (0.14-0.41)	0.21 (0.12-0.39)
Secondary effects		
Adalimumab vs infliximab	0.51 (0.41-0.64)	0.54 (0.42-0.69)
Crohn's vs UC	0.73 (0.56-0.95)	0.67 (0.50-0.91)
Previous anti-TNF (yes vs no)	1.61 (1.30-1.98)	1.64 (1.28-2.11)
Hospitalizations (yes vs no)	0.88 (0.78-0.99)	0.91 (0.80-1.05)
Surgeries (yes vs no)	1.12 (0.86-1.46)	1.28 (0.94-1.75)
Albumin (per increase of 1 g/dL)	-	0.95 (0.73-1.23)
CRP (per increase of 1 mg/dL)	-	1.03 (1.02-1.04)
Corticosteroids (yes vs no)	1.14 (0.89-1.48)	1.08 (0.80-1.46)
Methotrexate (yes vs no)	0.88 (0.61-1.28)	0.72 (0.46-1.14)
Thiopurines (yes vs no)	0.69 (0.56-0.86)	0.72 (0.56-0.93)

aHR, adjusted hazard ratio; CI, confidence interval; CRP, C-reactive protein; BLI, beta lactamase inhibitors

Supplementary table 6 Comparison of baseline variables between patients with available ADA levels that were included in our analysis and a frequency matched groups on treatment year in a 1:2 ratio of patients that did not have available ADA levels.

Variable	With available ADA (n=1,946)	No available ADA (n=3,887)	P value
Age, years	23 (19)	26 (20)	<0.001
Male, n (%)	909 (47)	1,768 (45)	0.39
BMI, kg/m²	22.2 (6.2)	22.9 (6.6)	<0.001
Adalimumab, n (%)	1,065 (55)	2,344 (60)	<0.001
Prior anti-TNF, n (%)	567 (29)	1,120 (29)	0.82
Crohn's, n (%)	1,595 (82)	3,093 (80)	0.03
Prior related surgery	526 (27)	1,154 (30)	0.04
Recent prior hospitalizations	886 (46)	1,882 (48)	0.04
Lab results, median (IQR)			
Hemoglobin*, g/dL	12.8 (2.2)	12.9 (2.4)	0.06
WBC*, K/µL	7.3 (3.1)	7.2 (3.0)	0.91
Platelets*, K/µL	284 (118)	283 (111)	0.1
CRP*, mg/dL	0.9 (2.0)	1.0 (2.4)	0.01
Albumin*, g/dL	4.1 (0.6)	4.1 (0.6)	0.04
Prior/concomitant medications, n (%)			
Antibiotics	1,593 (82)	3,172 (82)	0.84
Corticosteroids	236(12)	411 (11)	0.08
Thiopurines	856 (44)	1,430 (37)	<0.001
Methotrexate	133 (7)	280 (7)	0.64
5-ASA	572 (29)	1,114 (29)	0.58

ADA, anti-drug antibodies; BMI, body mass index; WBC, white blood cells; CRP, C-reactive protein;

Supplementary table 7 Kruskal-Wallis multiple comparison p-values adjusted with the Benjamini-Hochberg adjustment method

Comparison	Adjusted p-value
Azithromycin - Cefuroxime	0.04
Azithromycin - Control	0.56
Cefuroxime - Control	0.09
Azithromycin - Germ free	0.01
Cefuroxime - Germ free	<0.001
Control - Germ free	0.004

FIGURE LEGENDS

Supplementary figure 1 Graphical summary of the survival analysis model design