Antibiotic Complications During the Treatment of *Mycobacterium ulcerans* Disease in Australian Patients.

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Abstract:

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Background

Antibiotics are recommended first-line treatment for *M. ulcerans* disease. Antibiotic toxicity is common in Australian patients, yet antibiotic complication rates and their risk factors have not been determined.

Methods

An analysis of severe antibiotic complications was performed using data from a prospective cohort of *M. ulcerans* cases managed at Barwon Health from 1/1/1998-30/6/2016. A severe antibiotic complication was defined as an antibiotic adverse event that required its cessation. Antibiotic complication rates and their associations were assessed using a Poisson regression model.

Results

337 patients were included; 184 (54.6%) males and median age 57 years (IQR 36-73 years). Median antibiotic treatment duration was 56 days (IQR 49-76 days).

Seventy-five (22.2%) patients experienced severe antibiotic complications after a median 28 days (IQR 17-45 days) at a rate of 141.53 per 100 person-years (95% CI 112.86-177.47). Eleven (14.7%) patients required hospitalization. Compared with rifampicin/clarithromycin combinations, severe complication rates were not increased for rifampicin/ciprofloxacin (RR 1.49, 95% CI 0.89-2.50, p=0.13) or rifampicin/moxifloxacin (RR 2.54, 95% CI 0.76-8.50, p=0.13) combinations, but were significantly increased compared to 'other' combinations (RR 2.53, 95% CI 1.13-5.68, p=0.03).

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In a multivariable analysis, severe complication rates were significantly increased with reduced estimated glomerular filtration rates (aRR 2.65, 95%CI 1.24-5.65 for EGFR 60-89 mls/min and aRR 1.31, 95%CI 0.49-3.53 for EGFR 0-59 mls/min compared with EGFR ≥90 mls/min, p<0.01) and female gender (aRR 2.15, 95%CI 1.38-3.30, p<0.01).

Conclusions

Severe antibiotic complications during *M. ulcerans* treatment are high with increased rates independently associated with reduced renal function and female gender.

Key words: *Mycobacterium ulcerans,* antibiotic treatment, complications, adverse effects, Australia.

Introduction:

Mycobacterium ulcerans (*M. ulcerans*) is an infectious disease causing necrotizing infections of skin and soft tissue that can cause significant morbidity, long-term disability and often result in reconstructive surgery and hospitalization at significant cost.[1-4]. Worldwide it is the third most common mycobacterial disease after tuberculosis and leprosy with the greatest disease burden found in rural and remote regions of west and central Africa.[5] The disease is endemic in coastal regions of Victoria, Australia,[6] where the incidence continues to increase, resulting in increasing community concern.

Antibiotics are the recommended first-line treatment for *M. ulcerans* disease and are highly effective in curing lesions and preventing recurrences, alone[7, 8] or combined with surgery.[9] Oral antibiotics have also reduced hospitalisations and the cost of treatment.[3] However, antibiotic treatment regimens for *M. ulcerans* are not without toxicity, and in the Barwon Health experience 16-33% of patients cease them early due to side effects, especially in elderly patients.[1, 9, 10] The toxicity is often severe and can include potentially life-threatening drug hypersensitivity, as well as severe rash or hepatitis, and leads to hospitalisation in up to 4% of cases.[1] Knowledge of the rates and risk factors for drug toxicity may help to predict and minimise the toxicity, and in turn improve the safety, effectiveness and acceptability of treatment. To date this research has not been comprehensively performed in an Australian population.

The aim of this study was to determine the incidence rate and risk factors for antibiotic toxicity in Australian patients treated for *M. ulcerans* disease. Some basic data on severe antibiotic side-effects for patients enrolled early in our cohort and included in this study have been previously published by our group.[1, 7, 9-11] However, this current study includes a much larger cohort of patients, includes some patients excluded from previous studies due to a lack of a treatment outcome at 12 months (not required for this study), and defines rates and examines risk fators for antibiotic complications.

Methods:

An analysis was performed on data from a prospectively collected cohort of all confirmed *M. ulcerans* cases managed at Barwon Health from 1/1/1998-30/6/2016. A *M. ulcerans* case was defined as the presence of a lesion clinically suggestive of *M. ulcerans* plus any of (1) a culture of *M. ulcerans* from the lesion, (2) a positive PCR from a swab or biopsy of the lesion, or (3) histopathology of an excised lesion showing a necrotic granulomatous ulcer with the presence of acid-fast bacilli (AFB) consistent with acute *M. ulcerans* infection.[12] Lesion size was determined by measuring the extent of lesion induration with a ruler and a WHO category was assigned according to published definitions.[5]

Standard drug dosages for adults included rifampicin 10 mg/kg/day (up to a maximum of 600 mg daily), ciprofloxacin 500 mg twice daily, moxifloxacin 400 mg once daily, clarithromycin 7.5 mg/kg twice daily (up to 500 mg twice daily), ethambutol 15 mg/kg/day and amikacin 15 mg/kg/day up to a maximum of one gram daily. Dosages of ciprofloxacin, clarithromycin and ethambutol were reduced in severe renal dysfunction [Estimated glomerular filtration rates (EGFR) ≤ 30 mls/min] according to Australian guidelines.[13] A severe complication of antibiotic therapy was defined as an adverse event attributed to an antibiotic that required its cessation as determined by the treating clinician. In cases where it was not possible to determine which antibiotic of a combination was responsible for the complication, both antibiotics were attributed with that complication. Antibiotics that were ceased due to perceived treatment failure prior to the recognition of paradoxical reactions in 2009[14, 15] were not considered as complications.

Immune suppression was defined as current treatment with immunosuppressive medication (eg. prednisolone) or active malignancy. EGFR was calculated using the CKD-EPI formula.[16] Due to the longitudinal nature of the study, calendar years were catagorised and included as a variable in the analyses to assess whether time periods had an effect on severe complication rates. The initial period

corresponded to the time before WHO published its first guidelines on antibiotics use for M. ulcerans treatment (1998-2004),[17] and the rest of the cohort time was divided into equal 4-year blocks (2005-2008, 2009-2012 and 2013-2016).

Data analysis:

Data was collected prospectively using Epi-info 6 (CDC, Atlanta) and analysed using STATA 12 (StataCorp, Texas, USA). Outcome data were censored at the time of an antibiotic reaction requiring cessation of an antibiotic or at the completion of antibiotic treatment. For overall antibiotic complication rates, data was censored at the first severe antibiotic complication in a patient. For individual severe antibiotic complication rates, data was included regardless of whether the antibiotic was used in the initial or subsequent regimens. A Kaplan-Meier curve was used to measure the cumulative incidence of first severe antibiotic complications, and to compare the cumulative incidence of first severe complications stratified by EGFR category, gender and age. A Poisson regression model was used to assess severe antibiotic complication rates and associations of variables with severe antibiotic complication rates. Crude rate ratios were determined by performing univariable analyses. An initial multivariable analysis comparing rate ratios was then performed for all patients including the variables sex and age a priori and all variables showing evidence of an association with rates of severe complications in the crude analysis (assessed by $p \leq 0.20$). To assess the associations with rates of severe complications related to single antibiotics, a further three multivariable poisson regression models were examined using the same variables, except that each model included only those patients who had been administered either one of rifampicin, clarithromycin and ciprofloxacin respectively. The p-values for assessing the strength of the association of each variable with the rate of complications, controlled for all the other variables in the model, were determined by the likelihood ratio test.

Ethics:

This study was approved by the Barwon Health Human Research and Ethics Committee. All previously gathered human medical data were analysed in a de-identified fashion.

Results:

Baseline characteristics:

Three hundred and thirty eight patients were commenced on antibiotics during the study period; one patient was lost to follow-up prior to the completion of antibiotic treatment and was not included. Therefore 337 patients were included in the study analysis. Baseline characteristics of the cohort can be seen in table 1; 184 (54.6%) were male and the median age was 57 years (IQR 36-73 years). 260 lesions (77.4%) were classified as WHO category 1, and at presentation 283 (84.0%) lesions were ulcers. EGFR rates were categorised as 0-59 mls/min in 36 (10.7%) patients, 60-89 mls/min in 123 (36.5%) patients, ≥ 90 mls/min in 156 (46.3%) patients and missing data in 22 (6.5%) patients.

Antibiotic Treatment:

The median duration of antibiotic treatment was 56 days (IQR 49-76 days). Initial antibiotic combinations used were rifampicin/ciprofloxacin in 166 (49.3%), rifampicin/clarithromycin in 143 (42.4%), rifampicin/moxifloxacin in 8 (2.4%) and 'other' regimens 20 (5.9%). 'Other' regimens included rifampicin/clarithromycin/ethambutol in 6 (1.8%), clarithromycin/ciprofloxacin in 3 (0.9%), varied combinations in 9 (2.7%) and monotherapy in 2 (0.6%) treatment episodes. Including antibiotics commenced as second-line treatment following cessation of one or more of the initial antibiotics due to severe complications, 330 (97.9%) treatment episodes included rifampicin, 186 (55.2%) ciprofloxacin, 179 (53.1%) clarithromycin, 12 (3.6%) ethambutol, 11 (3.3%) moxifloxacin, 8 (2.4%) amikacin and 5 (1.5%) azithromycin. Ethambutol was not used after 2003 and amikacin was not used after 2009.

Rate of severe complications:

Overall, 75 (22.2%) patients experienced a severe antibiotic complication that required cessation of at least one antibiotic (table 2). The median time from commencement of antibiotic treatment to the first severe complication was 28 days (IQR 17-45 days). Over 52.99 combined years on antibiotic treatment the rate of initial severe complications was 141.53 per 100 person years (95% CI 112.86-177.47). Eleven (14.7%) patients required admission to hospital to manage their severe complications.

For those treated with rifampicin, there were 50 severe complications over 54.38 combined years at a rate of 91.95 per 100 person years (95% CI 69.69-121.32). (table 2) For those treated with ciprofloxacin there were 33 severe complications over 28.59 combined years at a rate of 115.43 per 100 person years (95% CI 82.06-162.37). For those treated with clarithromycin there were 27 severe complications over 26.56 combined years at a rate of 101.67 per 100 person years (95% CI 72-148.25). For those treated with ethambutol there were 5 severe complications over 2.08 combined years at a rate of 240.3 per 100 person years (95% CI 100.02-577.32). For those treated with moxifloxacin there were 3 severe complications over 1.73 combined years at a rate of 173.65 per 100 person years (95% CI 56.01-538.42). For those treated with amikacin there were 3 severe complications over 0.47 combined years at a rate of 637.06 per 100 person years (95% CI 205.47-1975.26). For those treated with azithromycin there was 1 severe complication over 0.58 combined years at a rate of 171.48 per 100 person years (95% CI 24.16-1217.34).

The cumulative incidence of first severe complications for rifampicin, ciprofloxacin and clarithromycin are shown in figure 1, The specific severe complications associated with each antibiotic are listed in table 3.

Compared with the initial antibiotic combination of rifampicin and clarithromycin, there was no significant difference in the rate of severe complications for the combination of rifampicin and

ciprofloxacin (RR 1.49, 95% CI 0.89-2.50, p=0.13), or rifampicin and moxifloxacin (RR 2.54, 95% CI 0.76-8.50, p=0.13) but there was a significant increase in severe complications when compared to 'other' regimens (RR 2.53, 95% CI 1.13-5.68, p=0.03).

Risk factors for severe complications

In a univariable analysis examining all patients the variables gender, age, diabetes, WHO stage and EGFR category were all strongly associated with severe antibiotic complications (table 4). Kaplan-Meier curves showing the cumulative incidence of severe complications stratified by gender, EGFR category and age are shown in figure 2.

In a multivariable analysis examining all severe first antibiotic complications together and adjusting for age, gender, EGFR category, WHO lesion category, diabetes and time period, EGFR category and gender were associated with an increased rate of severe antibiotic complications (table 4). In a multivariate analysis examining severe complications only involving rifampicin, the factors independently associated with severe complications were EGFR category (p=0.01), gender (p<0.01) and WHO category (p=0.02). In multivariate analyses examining severe complications only involving clarithromycin, the factors independently associated with severe complications was gender (p=0.05), EGFR category (p<0.01) and time period (p=0.01). In a multivariate analysis examining complications only involving ciprofloxacin, the only factor independently associated with complications was gender (p<0.01).

Discussion:

In this study we have shown that despite its known effectiveness,[7, 8] there is a significant toxicity associated with the antibiotic treatment of *M. ulcerans* in an Australian population. More than one in five patients experienced an adverse effect severe enough to warrant cessation of an antibiotic, and a significant number required hospitalization to manage their toxicity. Reported adverse effects

associated with treatment in African populations appear less common.[8, 18] However this is likely influenced by significant differences between the populations – African cohorts are younger[19, 20] and have less co-morbidities and potential drug interactions.

Severe antibiotic complications occurred throughout the antibiotic course. However the median time to develop severe complications was 4 weeks, corresponding to the halfway point of the currently recommended 8-week course of treatment.[5, 21] We have recently published our experience where in selected patients shorter antibiotic treatment durations were found to be effective.[22] According to results in this current study, antibiotic courses shortened to 4-6 weeks offer the potential to avoid up to 50% of the severe antibiotic complications. We therefore advocate for further research on short course treatment to explore the possibility of reducing treatment toxicity.

Australian guidelines recommend that rifampicin be combined with either clarithromycin or a fluoroquinolone for treatment of *M. ulcerans*.[21] We found the severe complication rates of clarithromycin and ciprofloxacin to be similar, individually or in combination with rifampicin, and thus their toxicity rates don't justify the use of one over the other. However, despite only being used in a small number of patients, the higher severe complication rate associated with amikacin led to it not being used in our study population after 2009 and supports the recommended use of oral antibiotic regimens in preference to this injectable agent in current Australian guidelines.[21] Ethambutol was used in the early years of the study prior to the publication of antibiotic treatment guidelines which no longer recommended its use.[17, 23]

We found that reduced renal function was independently associated with an increased rate of antibiotic complications. This likely results from an increased accumulation of antibiotic.[24] Some of the antibiotics used are known to accumulate in those with renal dysfunction, and reduced dosage is recommended for those with EGFR ≤ 30 mls/min for ciprofloxacin, clarithromycin and ethambutol.[13] However dose

reductions are not recommended for rifampicin above EGFR 10 mls/min or for moxifloxacin.[13] In our study, complications were independently associated with even mild to moderate renal dysfunction (EGF < 90 mls/min).

We found that female gender was independently associated with an increased rate of antibiotic complications. The reasons for this are not clear, but others have found similar for fluoroquinolone antibiotics [25, 26] and for drug-induced hepatotoxicity during anti-tuberculosis treatment.[27, 28] One hypothesis is that it relates to lower average body weight in women, with higher complications occurring at lower body weights due to increased relative antibiotic dosage. However, although in our study there were increased numbers of women compared to men in the lower weight categories, in the subset of patients analysed with body weight available (n=93), on univariable analysis there was no association between lower weight categories and antibiotic complications (p=0.26).

We have previously shown that antibiotic treatment of *M. ulcerans* in elderly populations is associated with increased toxicity.[1] However, our current study suggests that age is not an independent risk factor for antibiotic complications. Similarly Carbonin et al have previously concluded that there was no evidence that age acts as an independent risk factor for adverse drug reactions.[29] More specifically, others have reported no increase in adverse reactions with the use of fluoroquinolones in the elderly.[25, 30] It is likely that the increased rate of drug reactions in the elderly is influenced by a reduction in their renal function, as this declines with age,[31] and this may lead to higher serum concentrations and a longer half-life for antibiotics.[32, 33] As such, caution should be exercised in elderly patients, as has been suggested for the use of fluoroquinolones by Stahlmann et al that as a result of likely reduced EGFR in the elderly: “patients over 80 years of age with a marked decrease in lean body mass are those for whom dosage adjustment should be considered.” [30] Additionally, as the commonly used drugs can

interact with other medication,[34, 35] and the elderly commonly have comorbidities requiring treatment, this may contribute to increased toxicity in this age-group.[36]

We advocate for further research to be undertaken involving pharmacokinetic and pharmacodynamic studies of frequently used antibiotics. It is important to determine whether reduced antibiotic dosages in those with identified risk factors for complications, such as EGFR rates ≤ 90 mls/min and female gender, could reduce the toxicity but maintain the effectiveness of antibiotic regimens in Australian patients. Furthermore, the safety and effectiveness of alternative agents with demonstrated effectiveness against *M. ulcerans* such as bedaqueline,[37] clofazamine,[38] and avermectins[39] could be explored to determine if their use may reduce treatment toxicity without compromising effectiveness.

There are some limitations to our study. Firstly, due to a large proportion of the patients having missing data for weight the accuracy of our findings with respect to this variable should be interpreted with caution. Secondly, we did not collect data on the use of co-medications, and therefore were unable to assess their effect on toxicity outcomes. Finally, as this is an observational study there may be unmeasured confounders that may have influenced the results. However the cohort is large, data is collected prospectively and rates of follow-up are very high supporting the validity of our findings.

Conclusions

Severe antibiotic complication rates during *M. ulcerans* treatment of Australian patients are high, occurring on average halfway through the currently recommended 8-week course, with increased frequency in those with reduced renal function and among females. Further research is required to reduce toxicity including exploring the safety and effectiveness of reduced antibiotic treatment duration, and modifying antibiotic treatment doses in identified high risk groups.

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Figure 1: Kaplan-Meier curves showing the cumulative incidence of first severe complications in patients for **a**) rifampicin, **b**) ciprofloxacin and **c**) clarithromycin.

Figure 2: Kaplan-Meier curves showing the cumulative incidence of first severe complications in patients stratified by **a**) EGFR category, **b**) gender and **c**) age.

Table 1: Baseline patient characteristics

	n (%)
Gender	
male	184 (54.6)
female	153 (45.4)
Age category (years)	
0-15	35 (10.4)
16-64	170 (50.5)
≥65	132 (39.2)
WHO category of lesions	
1	261 (77.5)
2	39 (11.6)
3	37 (11.0)
EGFR category (mls/min)	
0-59	36 (10.7)
60-89	123 (36.5)
≥ 90	156 (46.3)

Missing	22 (6.5)
Lesion type	
Ulcer	283 (84.0)
Nodule	20 (5.9)
Oedema	30 (8.9)
Plaque	4 (1.2)
Co-morbidities	
Diabetes	31 (9.2)
Immune suppression	30 (8.9)
Weight Category (kg)	
0-49	15 (16.1)
50-74	31 (33.3)
75-99	34 (36. 6)

≥ 100	13 (14.0)
Missing	244 (72.4)
Time Period	
1998-2004	23 (6.8)
2005-2008	59 (17.5)
2009-2012	115 (34.1)
2013-2016	140 (41.5)

Table 2: Severe antibiotic complications in the Barwon Health cohort 1998-2016.

Antibiotic	Number of patients experiencing a severe complication (%)	Median time of treatment to severe antibiotic complication (days, IQR)	Combined duration of treatment (years)	Rate of severe antibiotic complications (per 100 person-years, 95% CI)
Overall	75 (22.2)	28 (IQR 17-45)	52.99	141.53 (112.86-177.47)
Rifampicin	50 (15.2)	28 (IQR 19-42)	54.38	91.95 (69.69-121.32)
Ciprofloxacin	33 (17.7)	26 (IQR 18-36)	28.59	115.43 (82.06-162.37)
Clarithromycin	27 (15.1)	21 (IQR 8-45)	26.56	101.67 (69.72-148.25)
Ethambutol	5 (41.7)	30 (25-45)	2.08	240.30 (100.02-577.32)
Moxifloxacin	3 (27.3)	14 (9-39)	1.73	173.65 (56.01-

				538.42)
Amikacin	3 (33.3)	23 (14-26)	0.47	637.06 (205.47-1975.26)
Azithromycin	1 (20.0)	10 (N/A)†	0.58	171.48 (24.16-1217.34)

†N/A: not applicable

Table 3: Specific severe complications associated with individual antibiotics

	Rash	GIT†	Hepatitis	Renal	Blood	Tendonitis	Eye	Neurological
Rifampicin (n=50)	14	26	15	2	2‡	0	0	0
Ciprofloxacin (n=33)	7	20	6	2	0	7	0	0
Clarithromycin (n=27)	7	18	6	0	0	0	0	2§
Moxifloxacin (n=3)	0	2	1	0	0	0	0	0
Ethambutol (n=5)	0	3	0	0	0	0	2	0
Amikacin (n=3)	0	0	0	0	0	0	0	3¶
Azithromycin (n=1)	1	0	0	0	0	0	0	0
Total patients	19	42	17	2	2	7	2	5

†GIT: gastrointestinal intolerance; ‡ thrombocytopenia; §one paranoia/depression; one deafness
¶ataxia or deafness

Table 4: Poisson regression model showing adjusted and unadjusted associations between identified factors and overall severe antibiotic complication rates.

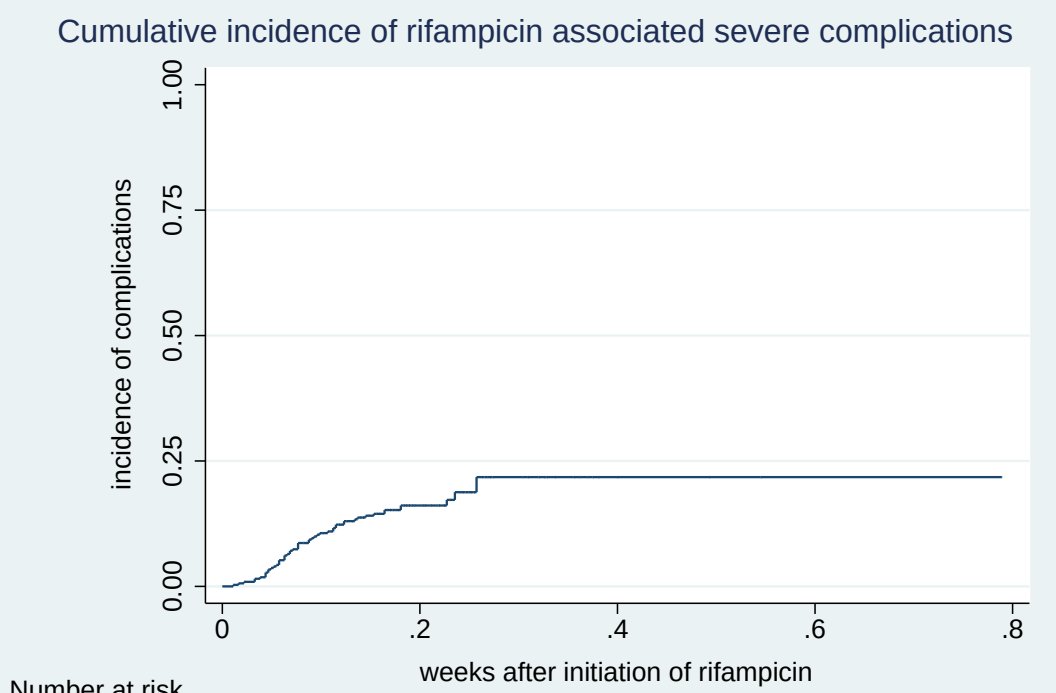
Variable	Failures (%)	Follow-up (years)	Rate per 100-person years (95% CI)	Crude rate ratio (95% CI)	p-value	Adjusted rate ratio (95% CI)[†]	p-value
Sex							
Male	31 (16.85)	30.61	101.27 (71.22,144.00)	1	<0.01	1	<0.01
Female	44 (28.76)	22.38	196.59 (146.30,264.17)	1.94 (1.23,3.07)		2.05 (1.38,3.30)	
Age (years)							
0-15	3 (8.57)	6.35	47.25 (15.24-146.51)	1	<0.001	1	0.17
16-64	20 (11.76)	26.42	75.69 (48.83,117.32)	1.60 (0.48,5.39)		1.28 (0.36,4.56)	
≥65	52 (39.39)	20.22	257.15 (195.95,337.46)	5.44 (1.70,17.43)		2.30 (0.58,9.10)	
WHO category of lesion							
1	58 (22.31)	40.32	143.85	1	<0.01	1	0.10

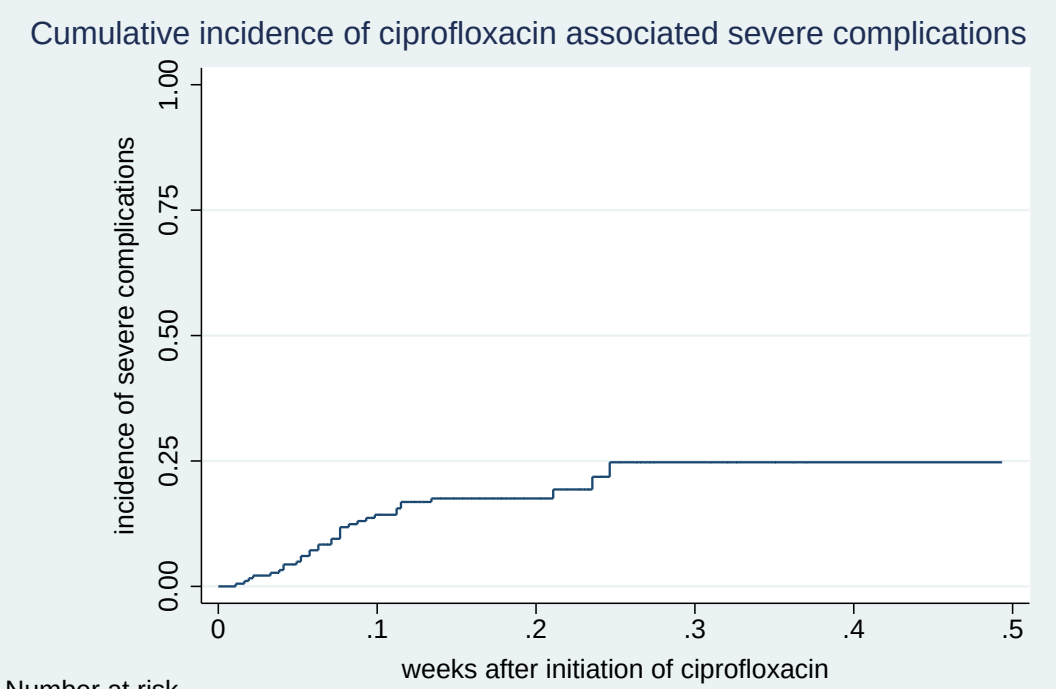
			(111.21,186.07)				
2	3 (7.69)	7.02	42.75 (13.79,132.56)	0.30 (0.09,0.94)		0.37 (0.11,1.22)	
3	14 (37.84)	5.66	247.51 (146.59,417.91)	1.71 (0.95,3.07)		1.30 (0.70,2.40)	
Lesion type							
Ulcer	60 (21.20)	43.44	138.12 (107.24,177.88)	1	0.49	-	-
Nodule	6 (30.00)	3.18	188.44 (84.66,419.43)	1.36 (0.59,3.16)		-	-
Oedema	9 (30.00)	5.72	157.29 (81.84,302.29)	1.14 (0.57,2.29)		-	-
Plaque	0 (0.00)	0.65	-	-		-	-
Immune suppression							
No	67 (21.82)	48.18	139.06 (109.45,176.68)	1	0.64	-	-
Yes	8 (26.67)	4.81	166.21 (83.12,332.36)	1.20 (0.57,2.49)		-	-
Diabetes							

No	62 (20.26)	47.97	129.25 (100.77,165.78)	1	0.04	1	0.60
Yes	13 (41.94)	5.02	258.76 (150.25,445.63)	2.00 (1.00,3.64)		1.19 (0.64,2.20)	
Estimated glomerular filtration rate (mls/min)							
≥ 90	15 (9.62)	24.89	60.26 (36.33,99.95)	1	<0.001	1	<0.01
60-89	48 (39.02)	18.51	259.35 (195.44,344.15)	4.30 (2.41,7.68)		2.65 (1.24,5.65)	
0-59	11 (30.56)	5.79	190.05 (105.25,343.18)	3.15 (1.45,6.87)		1.31 (0.49,3.53)	
Missing	1 (4.55)	3.81	26.28 (3.70,186.54)	0.44 (0.58,3.30)		0.41 (0.05,3.18)	
Weight (kg); n=93							
0-49	1 (6.67)	2.69	37.16 (5.23,263.78)	1	0.26	-	-
50-74	8 (25.81)	4.14	193.25 (96.65,386.43)	5.20 (0.65,41.59)		-	-
75-99	4 (11.76)	4.83	82.87 (31.10,220.80)	2.23 (0.25,19.95)		-	-
≥ 100	3 (23.08)	1.67	179.93	4.84		-	-

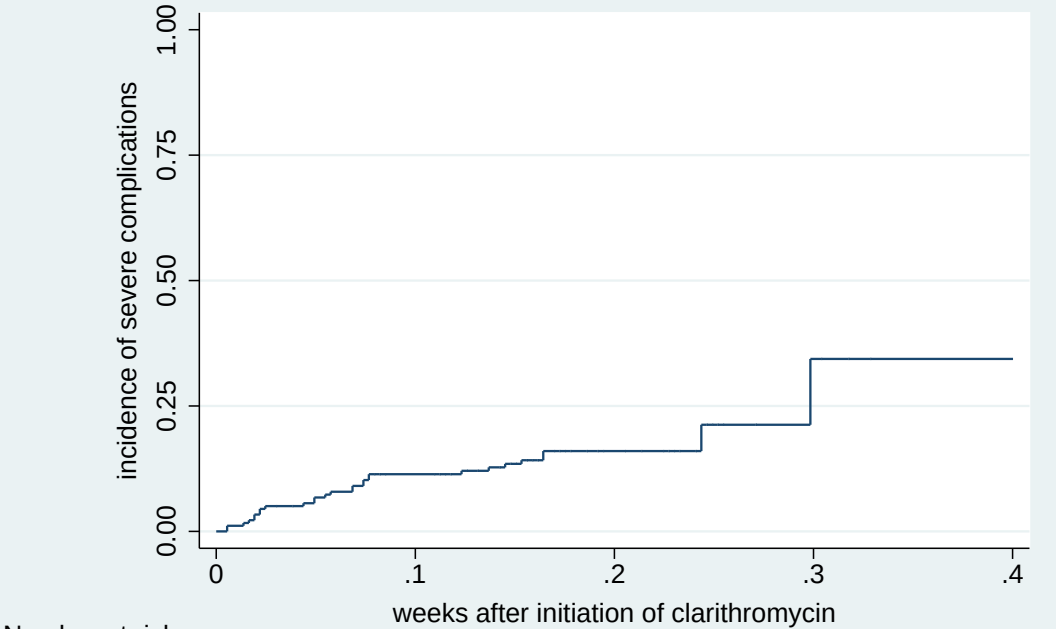
			(58.03,57.87)	(0.50,46.55)			
Missing	59 (24.18)	39.67	148.73 (115.24,191.96)	4.00 (0.55,28.89)		-	-
Time period							
1998-2004	11 (47.83)	3.89	282.94 (156.69,510.91)	1	0.13	1	0.70
2005-2008	18 (30.51)	11.49	156.65 (98.70,248.63)	0.55 (0.26,1.17)		0.68	
2009-2012	21 (18.26)	18.17	115.57 (75.35,177.25)	0.41 (0.20,0.85)		0.64	
2013-2016	25 (17.86)	19.44	128.57 (86.88,190.28)	0.45 (0.22,0.92)		0.78	

† Adjusted for sex, age, WHO category of lesion, Diabetes, EGFR category and time period.

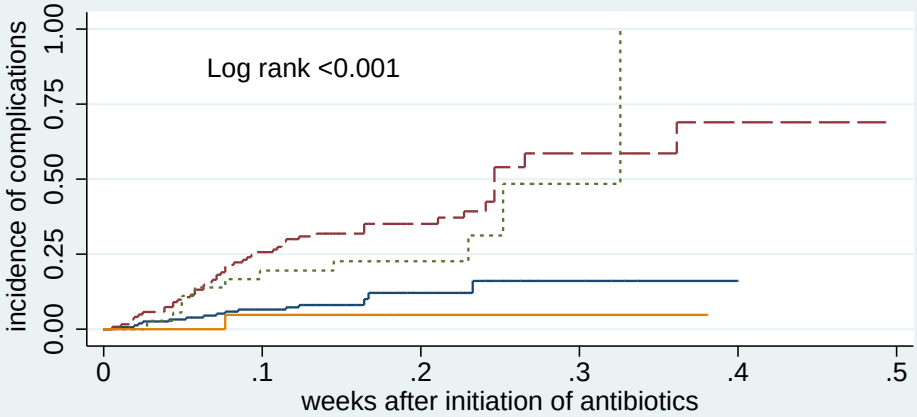




Cumulative incidence of clarithromycin associated severe complications



Cumulative incidence of first severe antibiotic complications

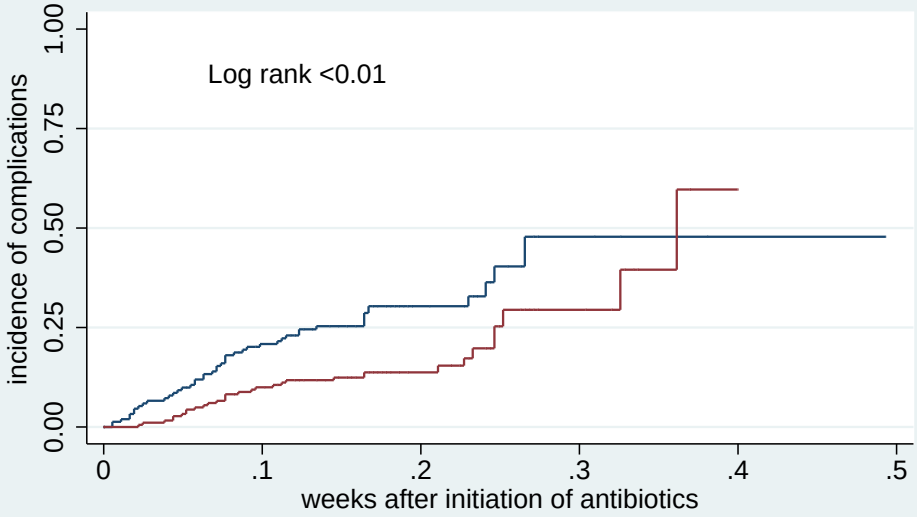


Number at risk

EGFRcat = 1	156	131	35	6	0	0
EGFRcat = 2	123	87	31	6	1	0
EGFRcat = 3	36	28	9	1	0	0
EGFRcat = 4	22	18	7	1	0	0

EGFRcat 1: >=90 EGFRcat 2:60-89
EGFRcat 3: 30-59 EGFRcat 4: <30

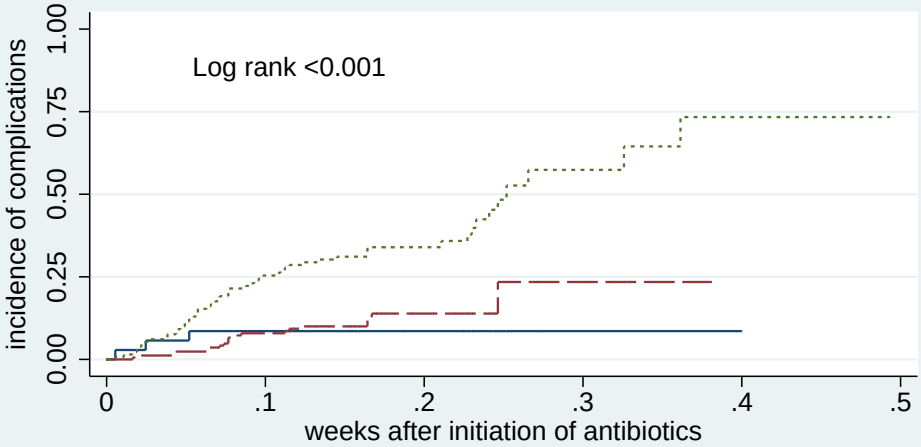
Cumulative incidence of first severe antibiotic complications



Number at risk

SEX = 0	153	111	31	5	1	0
SEX = 1	184	153	51	9	0	0

Cumulative incidence of first severe antibiotic complications



Number at risk

agegrp = 1	35	32	15	1	0	0
agegrp = 2	170	138	32	7	0	0
agegrp = 3	132	94	35	6	1	0

agegrp 1: 0-15 — agegrp 2: 16-64 — agegrp 3: >=65