Impact of antibiotic timing on mortality from Gram negative Bacteraemia in an English District General Hospital: the importance of getting it right every time

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Running Title: Antibiotic timing in Gram negative bacteraemia

Abstract

Objectives

There is limited evidence that empirical antimicrobials affect patient-oriented outcomes in Gram-negative bacteraemia. We aimed to establish the impact of effective antibiotics at four consecutive time points on 30-day all-cause mortality and length of stay in hospital.

Methods

We performed a multivariable survival analysis on 789 patients with *Escherichia coli*, *Klebsiella spp* and *Pseudomonas aeruginosa* bacteraemias. Antibiotic choices at the time of the blood culture (BC), the time of medical clerking, 24 and 48 hours post BC were reviewed.

Results

Patients that received ineffective empirical antibiotics at the time of the BC had higher risk of mortality before 30 days (HR 1.68, 95% CI 1.19 – 2.38, p=0.004). Mortality was higher if an ineffective antimicrobial was continued by the clerking doctor (HR 2.73, 95% CI 1.58 - 4.73, p<0.001) or at 24 hours from the BC (HR 1.83, 95% CI 1.05 – 3.20, p=0.033), when compared to patients who received effective therapy throughout. Hospital onset infections, 'high inoculum' source of infections, elevated C- reactive protein, lactate, and the Charlson Comorbidity index were independent predictors of mortality. Effective initial antibiotics did not statistically significantly reduce hospital length of stay (-2.98 days, 95% CI -6.08 to 0.11, p=0.058). The primary reasons for incorrect treatment were *in vitro* antimicrobial resistance (48.6%), initial misdiagnosis of infection source (22.7%) and non-adherence with hospital guidelines (15.7%).

Conclusion

Consecutive prescribing decisions affect mortality from Gram-negative bacteraemia.

Introduction

Gram-negative bacteraemia (GNB) is an increasingly common cause of community and hospital acquired sepsis. It usually refers to the growth of any aerobic Gram-negative bacillus in a blood culture but definitions in the literature vary. Between 12 and 38 percent of patients die within 30 days of infection.[1,2] These infections pose serious therapeutic problems due to the rising incidence of resistance to main antibiotic classes, leading to increasing reliance on broad-spectrum antibiotics.[3] The current 'gold standard' for treatment is early, empirical, effective antimicrobial treatment, which usually constitutes of monotherapy or combinations of beta-lactams/beta-lactamase inhibitors, aminoglycosides, fluroquinolones and carbapenems.[4,5] However, the effectiveness of this is not well established.

The impact of empiric antibiotic treatment on clinical outcome has been studied primarily in the context of sepsis. Amongst this cohort of patients, delays in initiating active antibiotics have been linked to increased risk of death and increased length of hospital stay.[4] However, these studies are not easily generalizable to patients with GNB: not all septic patients are bacteraemic and vice versa. Moreover, cohorts of septic patients often include infections due to Gram positive and other organisms. To date, no randomized controlled trials have evaluated empirical antibiotic regimens for GNB specifically.

As a result, current treatment recommendations are based on indirect data from sepsis as well as a small number of studies specifically addressing GNB.[6–19] The evidence for early effective treatment is currently inconclusive, as some studies report favorable outcomes[7,12–18] while other studies do not.[8–11,19] Conflicting results are also seen in studies looking at all types of bacteraemia.[18,20] A meta-analysis attempt in 2007 was not possible due to severe heterogeneity of the methodology of different studies, particularly with regards to the definition of appropriate treatment.[21] A different meta-analysis in 2015 concluded that effective antimicrobial treatment reduces mortality but included non bacteraemic infections.[22] *Lodise et al* in 2018 performed a meta-analysis of 20 papers with primarily *E.coli* and *Klebsiella* bacteraemias and demonstrated that delayed treatment increases mortality.[23] However, the included studies almost exclusively focused on ESBL pathogens, therefore limiting generalizability of results. All studies highlighted the differences in definitions used.

At present no studies have looked at the effect of consecutive clinical decisions on the outcome of patients with GNB. The objective of this retrospective observational cohort study was to explore the effect of prescribing decisions at specific time points on the mortality and length of stay in hospital of patients with GNB caused by *Escherichia coli* (*E.coli*), *Klebsiella spp* (*Klebsiella*) and *Pseudomonas aeruginosa* (*P.aeruginosa*). It also aimed to identify the reasons behind ineffective prescribing in these infections.

Materials and Methods

Ethics

As agreed with the local research and development department, no formal National Health Service (NHS) Health Research Authority approval was sought, as this project falls under service evaluation.

Setting and study population

This study was conducted in Wexham Park Hospital, a 600-bed district general hospital in Berkshire, England.

The inclusion criterion was any case of *E. coli, Klebsiella and P. aeruginosa* bacteraemia between the 1st of April 2017 and the 31st of March 2019. Cases were identified by local measures for mandatory Public Health England surveillance reporting. Patient data for each case were extracted from the hospital's electronic databases, pooled and validated by two investigators. When extracting data, investigators were blinded to patient outcome. Exclusion criteria included patients less than 18 years old, polymicrobial infections involving Gram positives, anaerobes or fungi (but not bacteraemias where all organisms were Gram negative) and recurrent bacteraemias within one month. To detect a 10% difference in mortality (12% versus 22%) between effective and ineffective treatment with a power of 90%, a sample size of 760 bacteraemias was calculated to be required, assuming an enrollment ratio of 3:1.

Outcomes

The primary outcome was all cause mortality by 30 days from the day of the BC, confirmed through the hospital information system, which includes post discharge deaths. The secondary outcome was length of stay in hospital, calculated as the time in days from the index BC to hospital discharge, for patients that survived their admission.

Definitions

Four assessors, blinded to patient outcome, independently assessed the effectiveness of the antimicrobial regime at four consecutive time points (at the time of the BC, the time of specialty (clerking doctor) review upon admission into hospital (usually between 6 and 12 hours after the BC), 24 hours post BC and 48 hours post BC) to reach a consensus. The effectiveness of all decisions after the initial antibiotics was studied in conjunction with the effectiveness of the initial antibiotics, forming 4 distinct subgroups (effective/effective, ineffective/effective, effective/ineffective and ineffective/ineffective antibiotics). All decisions were considered empirical (even if previous clinical samples like recent urine cultures or current Gram stain results were available), as full sensitivity results are not reported by 48 hours after the BC. For the length of stay analysis, only the effect of initial antimicrobials was studied.

Effectiveness of antimicrobial therapy was determined by *in vitro* susceptibility results using EUCAST breakpoints. First line sensitivities are by disk diffusion, extended sensitivities are determined by VITEK 2. For ESBL strains, conventional penicillins were considered ineffective treatment regardless of in *vitro* sensitivities if the patient was septic. For carbapenemase-producing strains, all classical β-lactams were considered ineffective. Oral treatment was considered effective only for antibiotics with high oral bioavailability (quinolones, folate synthesis inhibitors). For polymicrobial infections, treatment was considered effective only if antimicrobials administered were active against all pathogens in the BC.

Polymicrobial bacteraemia was defined as the growth of more than one microorganism in a BC. Source of infection was defined according to CDC criteria[24] and categorized to low inoculum (urinary tract infections, central venous catheter infections) and high inoculum (all others), as described in the BSIMRS score.[25] Hospital onset infections were defined as those detected 48 hours or more after admission to hospital.

Comorbidity burden was assessed using the age adjusted Charlson Comorbidity index (CCI). Severity of disease was assessed using a modified version of the National Early Warning score 1 (NEWS) at the time when the BC was taken. Oxygen requirement and confusion were excluded due to recording bias in emergency department documentation. C-reactive protein (CRP) and white cell count (WBC) values were collected at the time of the BC or within 24 hours. Lactate measurements were collected within 4 hours of the BC.

Statistical analysis

Multivariable Cox and linear regressions were used respectively for mortality and length of stay analysis in SPSS.[26] Parameters for the models were chosen based on statistical significance and model fitness as determined by the Bayesian Information Criterion additional to the R squared value for linear regression. Clinical judgement and knowledge of known risk factors from the literature were also utilized when deciding the final parameters. Fisher's exact test, Student t-test and Kruskal Wallis test were used to univariably compare variables as appropriate. To replace missing data in CRP (0.38%), WBC (5.7%), lactate (24.2%) and NEWS score (11.7%), 25 multiple imputations were performed.[27] Sensitivity analyses were also performed using complete case analysis. The level of statistical significance was set at 0.05.

Results

Out of the total 881 eligible patients, 789 were included in the final analysis (Figure 1). Missing data on the antibiotic regime were the reason for exclusion for only 24 patients (2.7%). Resistance profiles were available for all included patients. The overall mortality rate at 30 days was 18.1% (143/789). At the time of the BC, 72% of patients received effective treatment. That percentage increased to 77.1% after assessment by the clerking doctor, 87.3% at 24 hours and 92.8% at 48 hours. Table 1 demonstrates the differences in baseline characteristics between patients who died by 30 days versus patients who did not.

In multivariable survival analysis, ineffective antimicrobial treatment at time of the BC was associated with increased risk of death before 30 days (HR 1.68, 95% CI 1.19 – 2.38, p = 0.004, Figure 2a). Other factors significantly associated with increased mortality were hospital onset infections, high inoculum infections, elevated CRP, lactate and CCI (Table 2). The adjusted NEWS score and type of bacterium (*E.coli* versus *Klebsiella/Pseudomonas* versus polymicrobial), did not reach statistical significance but the NEWS score improved model fitness. Age, sex, WBC and ESBL status were not significantly associated with increased mortality nor improved model fitness. Therefore, they were not included in the final model.

Subsequent choices of antimicrobial treatment also affected patient outcome before 30 days. Patients who received ineffective treatment both initially and by the clerking doctor had greater mortality than patients who received effective antibiotics at both time points (HR 2.73, 95% CI 1.58 - 4.73, p <0.001, Figure 2b). Similarly, patients who received ineffective antibiotics initially and at 24 hours also had higher mortality when compared with patients who only received effective treatment throughout (HR 1.83, 95% CI 1.05 – 3.20, p = 0.033, Figure 2c). Higher risk of mortality was detected for patients that only had one correct decision in the two time points when compared to patients that received effective therapy throughout, but the difference was not statistically significant (Table 3). Patients receiving ineffective antimicrobial treatment at 48 hours had non-significant poorer outcomes at 30 days (Figure 2d). For all results, sensitivity analysis showed similar results for complete cases and cases with imputed values.

When an effective regime was prescribed at the time of the BC, the unadjusted risk ratio of clerking doctors prescribing effective treatment was 2.07 (95% CI 1.72 - 2.48, p <0.001). Similarly, when the previous clinician prescribed effective treatment, the patient was 1.92 times more likely to be receiving effective treatment at 24 hours (95% CI 1.67 - 2.21, p < 0.001). The same domino effect was observed for decisions taken at 24 hours (1.99 times increase at 48 hours, 95% CI 1.59 - 2.5, p <0.001).

Overall, the most common reason of ineffective treatment was antimicrobial resistance (242/498, 48.6%). Other reasons included initial misdiagnosis of the infection site as being

lung or skin, leading to prescription of antibiotics with Gram-positive spectrum only (113/498, 22.7%) and nonadherence to Trust guidelines (78/498, 15.7%). Finally, some patients received no antibiotics or oral antibiotics with low/moderate oral bioavailability (65/498, 13%).

For the length of stay analysis, 664 patients who survived their admission were included. In multivariable linear regression, effective antibiotic treatment was not associated with a significant change in length of stay by a small statistical margin (-2.98 days, 95% CI -6.08 - 0.11, p = 0.058). The most parsimonious model included age (+0.17 days per year older, 95% CI 0.09 - 0.25, p <0.001), CRP (+0.02 days per mg/dL higher, 95% CI 0.008 - 0.032, p = 0.001) and onset of infection (+13.55 days for hospital onset infections, 95% CI 9.54 - 17.57, p <0.001). It should be noted that the adjusted R squared value for our model was 0.095. Therefore, length of stay is primarily dependent on factors not studied here (likely frailty and social factors).

Discussion

We have undertaken a detailed retrospective observational study of patients with GNB assessing the importance of appropriate empiric antibiotic treatment at four specific time points. To our knowledge, this is the first study to look at consecutive prescribing decisions in this field. Our results demonstrate a survival advantage for patients who received early effective antibiotic treatment compared with those who did not, as well as for patients who had sustained administration of effective antibiotics.

This study highlights the importance of the Getting It Right First Time NHS improvement programme (GIRFT): the initial choice of antimicrobials is critical for survival and can have a domino effect on subsequent decisions, yet is often made by junior clinicians. Subsequent results also hinted that effective antimicrobials at any time point might improve patient outcome irrespective of previous treatment given. This constitutes a valuable finding, as it suggests that reviewing empiric regimes even 48 hours after the detection of GNB is of clinical significance, urging clinicians to “get it right every time”. Our study was underpowered to provide a definitive answer to these secondary outcomes, as we underestimated the percentage of patients that receive effective treatment at 24 and 48 hours. Studies adequately powered to further address this question should be conducted in the future, facilitated by our findings that will allow accurate sample size calculation for individual subgroups.

We used a more pragmatic approach to answer the question in hand: previous studies define effective treatment as at least one dose of effective antimicrobials within 24, 48 or 72 hours of the blood culture[8,10,11,13–15,17–19], or by the time the culture is declared positive.[7,9] This approach may lead to bias, as a substantial proportion of patients with bacteraemia are septic. Literature suggests that for these patients, every hour without effective treatment can affect mortality.[4] Therefore, patients that received effective treatment late in the 24-hour window would be classified as having had effective treatment, when in fact their outcome would be more guarded compared to if they had had effective treatment immediately. Our approach is not affected by this limitation. It also accounts for the fact that, in our clinical experience, antibiotic regimes frequently change when the patient is moved between clinical teams. Our approach captures these changes and the effect they have on patient outcome.

Few studies have aimed to examine the reasons behind ineffective antimicrobial therapy. In our cohort, antimicrobial resistance (particularly to co-amoxiclav, gentamicin and piperacillin tazobactam) was responsible for half of the cases of treatment failure. This result is in concordance with findings from a recent large cohort study of bacteraemic patients from 131 hospitals across the USA, where 49% of *in vitro* discordant treatment was due to resistance.[28]

Both studies highlight the urgent need for point of care diagnostics to guide empirical treatment. A recent metanalysis suggests that this intervention can reduce mortality and length of stay in hospital.[29] This provides additional value to our findings: if effective empirical treatment can impact patient outcome even up to 48 hours after detection of bacteraemia, a wider window for the deployment of point of care/rapid diagnostics is present.

Our study has multiple methodological strengths. It was sufficiently powered to answer the primary question asked, had a low rate of missing data (2.7%), and there was no loss to follow up. We adjusted for potential confounding factors including disease severity and patient comorbidities as previously recommended.[21] The age adjustment in the CCI neutralized the effect of age seen by previous authors.[10] Multivariable Cox regression was used for survival analysis, which is the preferred model when dealing with censored data.[21] Statistical indicators and clinical judgement were used to decide the final parameters included in the model, which is preferable to automated forward or backward conditional models.

Limitations of our study include the retrospective design and the fact that it is a single center study. Most importantly, the latter prohibits generalization of the reasons for ineffective treatment. All-cause mortality, rather than infection attributed mortality, was used as an end-point, therefore some patients might have died due to non-infectious causes.[30] Adequacy of source control was not recorded nor adjusted for as a potential confounder. We included polymicrobial GNBs in our study population, inserting them into the regression model with a small fitness cost to ensure they do not introduce bias. A modified version of the NEWS score was used, which limits the absolute value of the hazard ratio calculated for this specific parameter. For the purposes of adjustment in our regression model, we have no reason to believe that the two groups studied were preferentially affected by this modification. Other markers of disease severity, like CRP and lactate, were also used. We did not ensure that the dosing of antimicrobials used was correct. However, in our Trust, prescriptions are reviewed daily by clinical pharmacists and guidelines with appropriate doses are easily accessible through a mobile application. Duration beyond 48 hours of effective or ineffective antibiotics and its impact on mortality was not assessed. EUCAST breakpoints for co-amoxiclav were increased in 2018, therefore some patients might have received ineffective treatment according to the latest criteria.

Our results corroborate previous publications and meta-analyses that suggest effective antimicrobials are associated with improved mortality in GNB, which is in line with common clinical experience.[22,23] Guideline authors and clinicians should be alerted to this result to ensure empirical treatment is given every time by clinicians who have access to up to date and easily accessible antimicrobial decision support tools and rapid diagnostic tests. This is particularly important for patients with other risk factors described, like hospital onset infections, high inoculum infections and multimorbidity.

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Transparency declarations

The authors have no conflicts of interest to declare.

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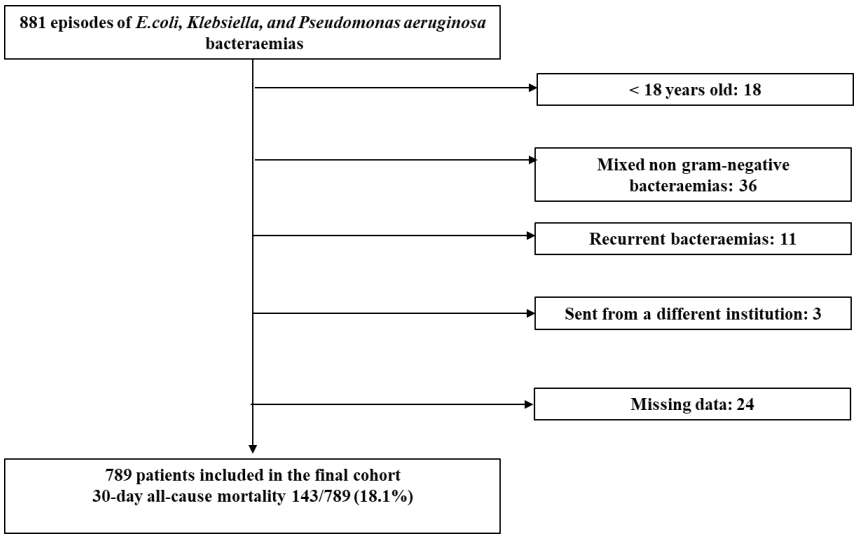

Figure 1: Patient flowchart

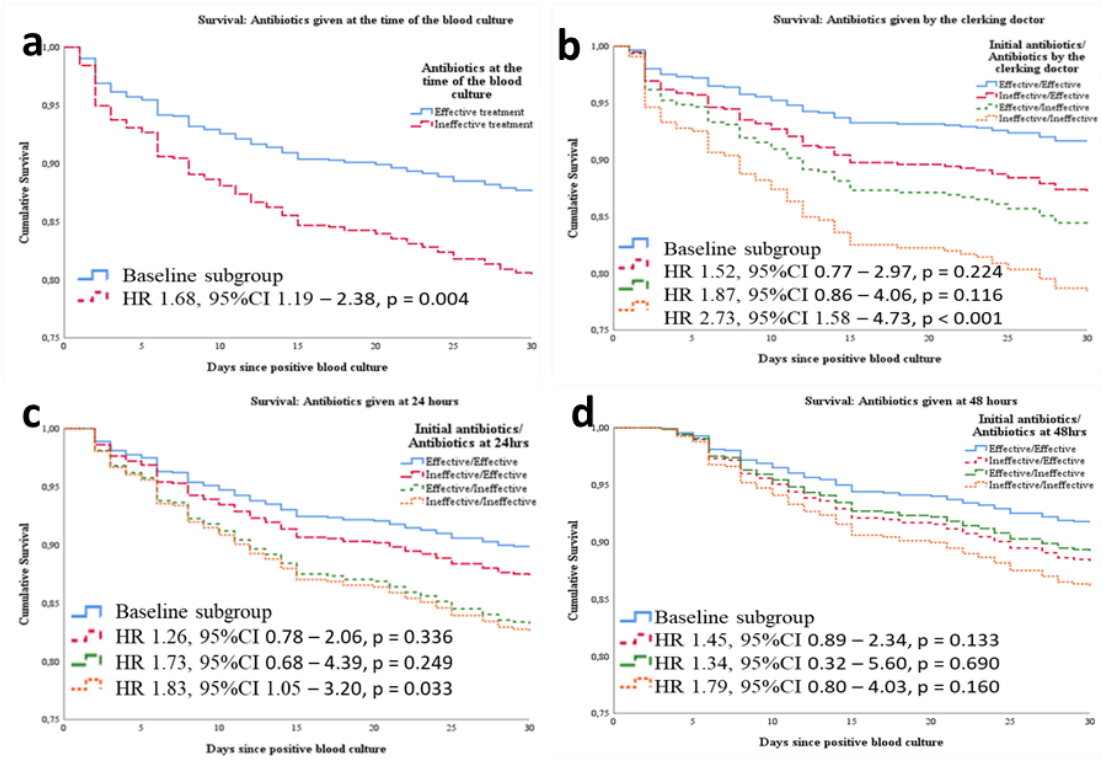

Figure 2: Survival graphs of patients receiving either effective or ineffective antimicrobial treatment at the four time points studied. Results adjusted for onset of infection, source of infection, CCI, CRP, lactate and type of bacterium. HR: Hazard ratio, CI: Confidence interval. This figure appears in colour in the online version of JAC and in black and white in the printed version of JAC.

Table 1: Baseline patient characteristics of the 789 patients included in the analysis

Clinical factor	Survivors (N = 646)	Non survivors (N = 143)	p-value[a]
Age in years (mean, standard deviation; SD)	71.7 (16.1)	76.6 (13.3)	< 0.001
Gender			
Male	334 (51.7%)	74 (51.7%)	1
Female	312 (48.3%)	69 (48.3%)	
CCI (median, interquartile range; IQR)	5 (3 – 7)	6 (4 -8)	< 0.001
Bacterium			
E. coli	503 (77.9%)	100 (69.9%)	
Klebsiella spp/P. aeruginosa	114 (17.6%)	31 (21.7%)	0.181
Polymicrobial	29 (4.5%)	12 (8.4%)	0.053
ESBL	69 (10.7%)	16 (11.1%)	0.882
Onset			
Hospital	85 (13.2%)	39 (27.3%)	< 0.001
Community	561 (86.8%)	104 (72.7%)	
Source			
High inoculum	266 (41.1%)	94 (65.7%)	< 0.001
Low inoculum	380 (58.9%)	49 (34.3%)	
Lactate mmol/L (mean, SD)[b]	2.23 (1.45)	3.63 (3.09)	< 0.001
CRP mg/dL(mean, SD)[b]	134.8 (112.8)	186.2 (107)	< 0.001
WBC x 10^9 cells (mean, SD)[b]	13.3 (7.8)	13.8 (11.5)	0.815
Adjusted NEWS score (median, IQR)[b]	4 (2 – 6)	5 (3 – 7)	< 0.001
Effective treatment at the time of BC	480 (74.3%)	88 (61.5%)	0.003
Effective treatment by the clerking doctor[c]	379/477 (79.5%)	52/82 (63.4%)	0.003
Effective treatment at 24 hours[d]	566/639 (88.6%)	88/110 (80%)	0.019
Effective treatment at 48 hours[e]	591/634 (93.2%)	78/87 (89.7%)	0.265

[a]Univariate comparisons and associated p values should not be interpreted as true correlations, as they are subject to significant confounding.
[b]Includes imputed values
[c]Only patients admitted though the emergency department (N = 559) are assessed by a clerking doctor.
[d]Forty patients had died by this time point (N=749).
[e]Sixty eight patients had died by this time point (N= 721).
CCI: Charlson Comorbidity Index, ESBL: Extended b-lactamase, CRP: C-reactive protein, WBC: White blood cell count

Table 2: Factors associated with risk of mortality in the final multivariable analysis

Variable	HR	95% CI	p-value
Treatment at the point of the BC (Ineffective versus effective)	1.68	1.19 – 2.38	0.004
Source (High versus low inoculum)	2.05	1.43 – 2.93	<0.001
Onset (Hospital versus Community)	1.89	1.28 – 2.78	0.001
CRP (per mg/dL higher)	1.003	1.001 – 1.004	<0.001
Lactate (per mmol/L higher)	1.18	1.12 – 1.25	<0.001
CCI (per point higher)	1.12	1.048 – 1.196	0.001
Adjusted NEWS score (per point higher)	1.05	0.98 – 1.13	0.165
Bacterium[a]			
Klebsiella spp/Pseudomonas	1.16	0.76 – 1.77	0.493
Polymicrobial	1.39	0.75 – 2.57	0.303

[a]Baseline *E. coli*, CCI: Charlson Comorbidity Index, CRP: C-reactive protein

Table 3: Consecutive treatment regimes – Individual subgroups hazard ratios

Treatment at the time of the BC	Treatment by the clerking doctor	N	Hazard ratio	95% CI	p-value
Effective	Effective	364		Baseline subgroup	
Ineffective	Effective	67	1.52	0.77 – 2.97	0.224
Effective	Ineffective	41	1.87	0.86 – 4.06	0.116
Ineffective	Ineffective	87	2.73	1.58 – 4.73	<0.001
Treatment at the time of the BC	Treatment at 24 hours				
Effective	Effective	518		Baseline subgroup	
Ineffective	Effective	136	1.26	0.78 – 2.06	0.336
Effective	Ineffective	27	1.73	0.68 – 4.39	0.249
Ineffective	Ineffective	68	1.83	1.05 – 3.20	0.033
Treatment at the time of the BC	Treatment at 48 hours				
Effective	Effective	506		Baseline subgroup	
Ineffective	Effective	163	1.45	0.89 – 2.34	0.133
Effective	Ineffective	18	1.34	0.32 – 5.60	0.690
Ineffective	Ineffective	34	1.79	0.80 – 4.03	0.160