Biomarker-guided antibiotic duration for hospitalized patients with suspected sepsis: The ADAPT-Sepsis Randomized Clinical Trial

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KEY POINTS

Question: Do critically ill adult patients hospitalized for suspected sepsis and treated with intravenous antibiotics based on procalcitonin (PCT) or C-reactive protein (CRP) protocols, have a safe reduction in treatment duration compared to standard care?

Findings: In this multi-center, randomized trial of 2,760 patients, the daily PCT-guided protocol reduced total antibiotic duration and had non-inferior all-cause mortality compared to standard care. No difference was found in total antibiotic duration between standard care and daily CRP-guided protocol, and CRP showed inconclusive results for all-cause mortality.

Meaning: In hospitalised adults, daily PCT-guided protocol reduces antibiotic duration safely compared to standard care, while daily CRP-guided protocol does not.

ABSTRACT

IMPORTANCE: For hospitalized critically ill adults with suspected sepsis, procalcitonin (PCT) and C-reactive protein (CRP) monitoring protocols can guide the duration of antibiotic therapy, but the evidence of the effect and safety of these protocols remains uncertain.

OBJECTIVES: To determine whether CRP or PCT safely results in a reduction in the duration of antibiotic therapy.

DESIGN, SETTING, AND PARTICIPANTS: A multi-center, intervention-concealed randomized controlled trial, involving 2, 760 adults (≥ 18 years), in 41 UK NHS intensive care units, requiring critical care within 24 hours of initiating intravenous antibiotics for suspected sepsis and likely to remain on antibiotics for at least 72 hours.

INTERVENTION: From January 2018 to June 2024, 918 patients were assigned to the daily PCT-guided protocol, 924 to the daily CRP-guided protocol and 918 assigned to standard care.

MAIN OUTCOMES AND MEASURES: The primary outcomes were total duration of antibiotics (effectiveness) and all-cause mortality (safety) to 28 days. Secondary outcomes included critical care unit data and hospital stay data. Ninety-day all-cause mortality was also collected.

RESULTS: Among the randomized patients (mean age 60.2 [SD, 15.4] years; 60% males), there was a significant reduction in antibiotic duration from randomization to 28 days for those on the daily PCT-guided protocol compared to standard care (mean duration 10.7 [7.6] days for standard care and 9.8 [7.2] days for PCT; mean difference [MD], 0.88 days; 95% Confidence Interval [CI], 0.19 to 1.58, P=0.01). For all-cause mortality up to 28 days, the daily PCT-guided protocol was non-inferior to standard care, where the non-inferiority margin was set at 5.4% (19.4% [170 of 878] on standard care, 20.9% [184 of 879] on PCT; absolute difference, 1.5 [95% CI, -2.18 to 5.32], P=0.02). No difference was found in antibiotic duration for standard care versus daily CRP-guided protocol (mean duration 10.6 [7.7] days for CRP; MD 0.09; 95% CI, -0.60 to 0.79, P=0.79). For all-cause mortality, the daily CRP-guided protocol was inconclusive compared to standard care (21.1% [184/874] on CRP; absolute difference, 1.7; [95% CI, -2.07 to 5.45], P=0.03).

CONCLUSIONS AND RELEVANCE: PCT reduces antibiotic duration safely compared to standard care, while CRP does not. All-cause mortality for CRP was inconclusive.

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INTRODUCTION

Delivering timely, appropriate antimicrobial therapy is an international care standard to help provide the best outcomes for patients with sepsis.[1] The optimum duration of antibiotic treatment for sepsis is uncertain, with decisions to stop therapy guided by clinical progress and serum inflammatory biomarkers such as serum C-reactive protein (CRP) and procalcitonin (PCT).[2] Optimizing antibiotics duration helps reduce overtreatment , limits unwanted effects and preserves antibiotic effectiveness by minimizing resistance.[3] Biomarker-guided discontinuation, especially with PCT, has shown safe reductions in antibiotic duration.[4] However, the body of clinical trial evidence has been judged to be low quality[1,5,6] leading to a weak recommendation for routine sepsis care adoption of PCT-guided antibiotic discontinuation[1] and with no consensus guidance for CRP.[1]

A three-group multi-center, intervention-concealed randomized controlled trial was performed to determine whether treatment protocols for monitoring CRP or PCT safely resulted in a reduction in the duration of antibiotic therapy for critically ill hospitalized adults with suspected sepsis. The primary aim was to assess reduction in antibiotic duration (clinical effectiveness) while maintaining treatment safety (non-inferiority) as measured by 28-day all-cause mortality.

METHODS

Trial Design and Oversight

The ADAPT-Sepsis trial was an investigator initiated, randomized clinical trial conducted in 41 National Health Service (NHS) intensive care units in UK. The trial protocol and amendments (Supplement 1) were approved by the South-Central Oxford and Scotland Research Ethics Committees (17/SC/0434) and the protocol has been published previously.[7] The statistical analysis plan was approved by the independent Data Monitoring and Ethics Committee (Supplement 2). The independent Trial Steering and Data Monitoring Committees oversaw the operational processes and statistical rigor of this study. All

patients or their legal representatives provided signed informed consent. Enrollment was paused during the UK lockdown (March-August 2020) due to the SARS-CoV-2 pandemic.

Patient Population

Eligible patients were hospitalized adults (≥18 years old) treated in ICU (i.e. admission to a Critical Care/Intensive Care Unit), within 24 hours of initiating intravenous antibiotics for suspected sepsis and likely to remain on antibiotics for at least 72 hours. 'Suspected sepsis' was defined as 'acute organ dysfunction associated with suspected infection'.[8] We did not mandate a definition for 'acute organ dysfunction' and patient information underpinning local clinical decisions were captured which included the Sequential Organ Failure Assessment (SOFA) score. A 24-hour recruitment window was required to determine baseline biomarkers for treatment guidance.[2,9] Patients were ineligible if they: (i) required prolonged antibiotic therapy (i.e. >21 days); (ii) were severely immunocompromised from a cause other than sepsis (e.g. neutropenia less than 500 neutrophils/µl); (iii) were expected to receive an IL-6 receptor inhibitors (e.g. tocilizumab or sarilumab) during their acute hospital admission; (iv) had sepsis treatments likely to stop within 24 hours because of futility; (v) declined consent; or (vi) were previously enrolled into this trial. Full inclusion and exclusion criteria are provided in Supplement 3.

Randomization

Patients were randomly assigned to standard care, PCT, or CRP groups in a 1:1:1 ratio using a computer-generated sequence (minimization method). Stratification factors were sepsis severity (shock or not)[8], recruitment site, and recent surgery (within 72 hours). Allocation was concealed by a centralized 24-hour web-based system (located at Warwick Clinical Trials Unit), with randomization conducted by site research staff.

Interventions

Blood was drawn daily in trial patients from randomization until antibiotic discontinuation for the sepsis episode or hospital discharge. Clinicians responsible for managing patients received daily standardized written advice from the local research team on either standard care or on biomarker-guided antibiotic discontinuation. Advice was based on daily serum testing of either (a) PCT or (b) CRP or (c) 'no test' (standard care group). Patients received standard NHS care for sepsis and antibiotic stewardship which followed national service standards.[10,11] The intervention phase consisted of daily research blood sampling and local NHS quality assured laboratory biomarker testing. Reporting of laboratory results was via a trial-specific centralized web-based system, leading to automated production of written treatment advice for the local clinical research team. The intervention phase continued until antibiotics were discontinued, or the patient died or withdrew. Follow-up phase began when daily blood collection stopped. Research blood sampling did not resume if antibiotics were re-introduced within 28 days. If a patient was discharged from hospital on a course of antibiotics for the initial sepsis episode, the trial intervention ceased at the time of discharge. Phlebotomy and samples followed local standard care practice. The antibiotic discontinuation protocols and advice are described in eTable 1.

Procalcitonin and C-reactive protein

For those assigned to the intervention arms, blood collection and serum biomarker laboratory testing (PCT or CRP) commenced within the first 24 hours of initiating intravenous antibiotics for sepsis. Based on evidence from national pre-trial surveys of standard critical care in the UK, described in our trial protocol[7], CRP, but not PCT, could be measured outside of the study protocol if deemed necessary by the clinician, but not used for protocolized antibiotic duration guidance. Daily patient reviews by the treating clinical team included documented decisions on antibiotic treatment guided by standard clinical assessment and review of microbiological culture results. Daily clinical reviews of patients also

allowed incorporation of the intervention protocols for daily assessment of antibiotic discontinuation described in eTable 1.

Standard care group

For the standard care group, daily research blood samples were collected and transported to the laboratory. No CRP or PCT biomarker testing was performed but there was standardized computer-generated treatment advice for the local clinical research team (eTable 1), time-delayed by the centralized web-based system to assure maintenance of group concealment.

Routinely available laboratory data, such as white blood cell counts remained part of standard care for each group.[10]

Intervention concealment

Group assignment was available to the local laboratory service only through the trial-specific web-based system, concealed from patients, their relatives, clinical teams and research staff. Research blood samples were allocated a unique research study number and were transported to the local hospital laboratory, until the antibiotics were discontinued. The research number did not reveal the identity of the patient and biomarker measurement results were not recorded in the patient's care record form or shared with the clinical team.

Procedure

The schedule of delivery and data collection are detailed in Supplement 3. Data were collected daily using a local paper clinical record form and a web-based data capture system. Ninety- day all-cause mortality status was collected from sites and validated against available linked NHS England mortality data. For patients discharged to another hospital or the community before day 28, the local site research team assured data completeness.[7] Disease severity was collected using the ICNARC (Intensive Care National Audit and Research Centre) Case Mix Program (England, Northern Ireland and Wales) and Scottish equivalent (Scottish Intensive Care Society Audit Group).

Outcomes

Primary outcomes

The primary clinical effectiveness outcome was the total antibiotic duration (days), from randomization to 28 days. The primary safety outcome was the 28-day all-cause mortality.

Secondary outcomes

Several secondary outcomes were evaluated and these included: (i) antibiotic duration for initial sepsis period; (ii) total antibiotic dose (Defined Daily Dose); (iii) antibiotic dose for initial sepsis period; (iv) unscheduled escalation care/re-admission; (v) infection relapse/recurrence requiring further antibiotic treatment; (vi) super-infection defined as new infection at a different anatomical site; (vii) suspected antibiotic adverse reactions; (viii) time to 'fit for hospital discharge'; (ix) critical care unit length of stay; (x) hospital length of stay; (xi) all-cause mortality at 90 days. Adverse events (see Supplement 3) and trial process data were also obtained. This manuscript reports clinical effectiveness outcomes; health economics and process evaluation will be detailed in subsequent publications.

Statistical Analysis

This study, using a sample size of 2,760 patients, aimed to detect a 1-day reduction in total antibiotic duration (standard care mean: 7 days, standard deviation (SD) 6 days, 90% power, 5% significance level, 5% withdrawal rate). The primary outcome focused on effectiveness, but safety was equally critical. For this reason this study aimed to show non-inferiority with a 5.4% safety margin (1-sided significance level: 2.5%[12,13]) assuming 28-day all-cause mortality of 15% in both arms (Supplement 1 details the justification of the choice in these parameter estimates). Analyses followed an 'intention-to-treat (ITT)' approach.[14] Each intervention arm was compared with standard care and no adjustments were made

for multiple comparisons for the primary effectiveness outcome. All statistical analyses were conducted in Stata SE version 18.0.[15]

The statistical analysis plan is provided in Supplement 2. For the primary outcome, linear mixed effect regression models were fitted, adjusted for age, sex and stratification factors (where recruiting site was a random effect). Several sensitivity analyses were carried out: (a) a per protocol analysis, where major protocol violations were excluded from the sample; (b) a complier average causal effect (CACE) analysis[16] adjusted for patients who withdrew from the intervention phase but remained in the study for follow-up ; (c) imputation analysis which accommodated for missing antibiotic treatment duration (Supplement 2); and (d) the Pocock's win ratio test[17] used to assess the competing risks of death, with death as the first event and duration of antibiotics as the second event, in the hierarchy of outcomes. Total duration of antibiotic therapy was displayed using Kaplan-Meier curves and Bayesian probabilities were also reported using an uninformative prior distribution.

The primary safety outcome was assessed using a mixed effect logistic regression model. From this model, 95% CIs in proportions between the treatments were obtained. For the adjusted models, the standard error was obtained using bootstrapping methods.[18,19] As per guidance for non-inferiority trials[20], inferiority was declared if P< 0.025 and the lower bound of the 95% confidence interval exceeded the margin.[12,13] A post-hoc per protocol analysis was also conducted (where per protocol was defined as for the primary analysis).

Secondary outcomes were analyzed using mixed effects linear and logistic regression models, with additional analyses for SARS-CoV-2 impact and serious adverse events. For the categorical outcomes, where absolute and relative differences were reported, bootstrapping methods [18,19] were used to

obtain the standard errors for the confidence intervals. Prespecified sub-group analyses included: (i) community-acquired pneumonia (yes/no) (ii) hospital-acquired pneumonia (yes/no) (iii) urinary tract infection (yes/no) (iv) intra-abdominal infection (yes/no) (v) positive blood culture infection (yes/no) (vi) community-acquired and hospital acquired infections (vii) SARS-CoV-2 (yes/no); (viii) sepsis and septic shock (ix) ward and critical care unit (intervention stopped); (x) surgery and non-surgery previous 72 hours. These sub-groups were carried out using the duration of antibiotics (i) up to 28 days and (ii) the initial sepsis period (post-hoc analysis). Sub-group analyses were conducted using linear regression models with interaction terms and 99% CIs.

RESULTS

Patient Characteristics

From January 2018 to June 2024 a total of 16,109 patients were screened for eligibility for the trial in 41 UK critical care units. Of these, 2,761 (17.1%) patients were enrolled into the study; one patient was removed due to an error in randomization. Of the remaining, 918 (33.3%) were assigned to standard care, 918 (33.3%) to the daily PCT-guided protocol and 924 (33.4%) to the daily CRP-guided protocol. 127 (4.6%) patients completely withdrew from the study prior to 28 days, and these were similar across the interventions (Figure 1 and eTables 9 & 12). In total, 364 (13.2%) patients withdrew from the intervention phase but remained in the study for follow-up (eTable 12).

Patients in the three groups had similar demographic and baseline characteristics (Table 1). The overall mean age was 60.2 [SD, 15.4] years, with 1,657 (60.3%) males. The mean APACHE (Acute Physiology and Chronic Health Evaluation) II score was 17.3 [SD, 6.5] and virtually all the patients would have met the Sepsis-3 criteria for the diagnosis of sepsis (SOFA score 7 [IQR 5-9])[8]. There were 1,397 (50.8%) sepsis and 1,352 (49.2%) septic shock patients.

Implementation of intervention protocols

Site monitoring revealed very low use of open PCT measurements (eTable 27) and there was no evidence of open protocolized daily CRP-guided antibiotic duration decisions in this intervention concealed trial. The daily PCT and CRP protocols were implemented into routine sepsis care, with concealed non-mandated advice on standard care and antibiotic discontinuation produced as summarized in Figure 3 (with additional data in eTable 29 & 30 and eFigures 6). No stop or strong stop advice was produced for the standard care group. Stop advice production was similar for both biomarker intervention groups. However, strong stop advice was more common and produced earlier for the PCT-protocol compared with the CRP-protocol.

Primary And Secondary Efficacy Outcomes

Primary outcome data were available on 898 (97.8%) patients for the daily PCT-guided protocol, 892 (96.5%) for the daily CRP-guided protocol, and 905 (98.6%) for standard care. Compared with standard care, there was a significant reduction in the total duration of antibiotic treatment from randomization to 28 days for the daily PCT-guided protocol (mean total duration was 10.7 (7.6) days for standard care and 9.8 (7.2) days for daily PCT-guided protocol; MD, 0.88 days; 95% CI, 0.19 to 1.58, P=0.01). No difference was seen between standard care and daily CRP-guided protocol (mean total duration was 10.6 (7.7) days for daily CRP-guided protocol; MD, 0.09 days; 95% CI, -0.60 to 0.79, P=0.79 (see Table 2 and Figure 2(a)). Results were similar in the adjusted analyses (eTable 18) and for all sensitivity analyses, including accounting for those who died within 28 days (Table 2). The Bayesian analyses illustrated that the probability of a mean difference in favor of the daily PCT-guided protocol of > 0.5 days was 0.85 and for daily CRP-guided protocol being >0.5 days was 0.13 respectively (see eTables 19 and 20 for further estimates).

There was also a significant reduction in the duration of antibiotics for the initial sepsis period, with the difference favoring the biomarker protocols as opposed to standard care (daily PCT-guided protocol: MD, 1.13 days; 95% CI, 0.58 to 1.68 and daily CRP-guided protocol: MD, 0.71 days; 95% CI, 0.16 to 1.26). For the other secondary outcomes, there was no statistical evidence in intervention effects when compared with standard care. Regarding additional analyses, the summary statistics for patients recruited pre-SARS-CoV-2 and post-SARS-CoV-2 are presented in eTable 22 and eTable 23. It is worth noting that there were only 19 trial patients included with a SARS-CoV-2 virus infection during the study.

Safety Outcomes

The 28-day all-cause mortality for the daily PCT-guided protocol was non-inferior to standard care (mortality: 19.4% (170 of 878) for standard care, 20.9% (184 of 879) for PCT; absolute difference, 1.57; 95% CI, -2.18 to 5.32 P=0.02; comparisons are made with P=0.025). However, the treatment difference for the daily CRP-guided protocol was inconclusive with regards to non-inferiority (mortality: 19.4% (170 of 878) for standard care, 21.1% (184of 874) for CRP; absolute difference, 1.69; 95% CI, -2.07 to 5.45; P=0.03) (Table 2 & eFigure 1). Results were supported by the per protocol (Table 2) and the adjusted analyses (eTable 18 & eFigure 1). There were nine serious adverse events equally distributed across the treatment and standard care arms (eTables 25 & 26). There were no differences in all-cause mortality at 90-days when comparing each intervention group with control (Table 2).

Kaplan-Meier survival curves show no differences when comparing each intervention group with standard care for all-cause mortality to day 28 (Figure 3B) and to day 90 (eFigure 7 in Supplement 3).

Pre-Specified Sub-Group Analyses

The effect of the two protocols on the duration of antibiotic treatment was not significantly modified by any of the baseline characteristics defining the prespecified subgroups (eFigures 2 and 3) and for the initial sepsis period (eFigures 4 and 5). Similar results were produced for unadjusted and adjusted sub-group analyses.

DISCUSSION

In hospitalized critically ill adult patients with suspected sepsis, a daily PCT biomarker-guided antibiotic discontinuation protocol, but not CRP-guided, resulted in safe reductions in total antibiotic duration when compared with standard care. Non-inferiority for 28-day all-cause mortality, our primary safety outcome, was met for the daily PCT-guided protocol.

Secondary outcomes suggest that antibiotic duration for the initial sepsis period was significantly reduced by both daily PCT-guided and daily CRP-guided protocols, with greater reductions for PCT. According to our primary outcomes, these initial antibiotic duration reductions are not present by the end of the trial period (28-days from randomization) for the daily CRP-guided protocol group, but there remain significant total antibiotic duration reductions for the daily PCT-guided protocol group, when compared with standard care. Supported by data on the implementation of our protocols , it is likely that these differential clinical effectiveness findings for daily PCT-guided and daily CRP-guided protocols are explained by the differences in the utility of these biomarkers to track inflammation caused by bacterial infection in the setting of critical illness, where PCT concentrations are known to increase earlier and normalize more rapidly than CRP in response to treatment.[21]

There are several important strengths to our study. This multi-center trial was designed to inform international guidance[1] for both daily PCT and CRP-guided antibiotic discontinuation protocols for sepsis. We successfully delivered an intervention concealment strategy to minimize risk of bias, rigorously testing biomarker-guided protocols within standard sepsis care and antibiotic stewardship. The vast majority of enrolled study patients would have met the Sepsis-3 criteria for the diagnosis of sepsis[8]. This trial addressed two important areas: 1. the use of total antibiotic duration from randomization to 28-days to embrace the possibility that biomarker-guided reductions in initial antibiotic duration for sepsis may result in later antibiotic use; and 2. the use of primary outcomes that embraced total antibiotic duration (effectiveness) and all-cause mortality (safety). The design of the biomarker protocols was informed by the best available evidence published in advance of the trial.[7]

The daily PCT-guided protocol's safe reductions in antibiotic duration, though seemingly modest, are equivalent to the current synthesized evidence for PCT-guided duration effects from open-label clinical trials using PCT.[4] The duration reduction is of the order of 10% in antibiotic use for sepsis, which could provide significant cost and labor savings, and might also reduce the development of antimicrobial resistance.

The trial protocol and concealed interventions provided high-quality evidence required to confidently assess biomarker-guided antibiotic protocols in standard sepsis care. However, there are a number of potential limitations to our study design. 1. It is possible that our concealment strategy could have led clinicians to stop antibiotics later in the standard care group while awaiting the return of stop advice. Reassuringly , our measured standard care antibiotic duration for the initial sepsis period was less than the synthesized standard care mean reported from current open label biomarker-guided trials[4]. 2. Patient-level randomization in this study could have led to contamination as treatment protocols and standard care were carried out in a shared environment. The complete elimination of these effects

would be challenging and not pragmatic in this care setting. A cluster-randomized trial design was considered initially, which resulted in a much larger sample size and other care process challenges, making the study infeasible and therefore this was not adopted. It is anticipated that, in this trial, a strategy to conceal group assignment and daily biomarker results, and the use of remote centralized hospital laboratories at each site, has gone to some way to eliminate the bias created by a potential for contamination. 3. It remains unclear whether allowing clinicians to monitor CRP as part of standard care, outside of the trial concealed daily biomarker protocols, impacted trial results. Any effects would have been mitigated by the intervention concealed nature of our trial and across all three randomized groups. Further analysis of this potential limitation is planned as part of a subsequent trial process evaluation. 4. For the pairwise comparisons, where treatment arms were compared to standard care, no statistical adjustments were applied to the results for multiple comparisons. Had we applied the correction retrospectively, where each pairwise comparison was based on a p-value of 0.025 (using a Bonferroni correction, for two tests), the conclusions of the study would not have altered.

The ADAPT-Sepsis trial strengthens substantially international recommendations for the routine use of protocolized daily PCT-guided antibiotic discontinuation in critically ill adults with sepsis.[1] and we found no evidence to recommend protocolized daily CRP-guided antibiotic discontinuation. We emphasize that critically ill patients recruited to this trial had already commenced antibiotics for sepsis, so this study does not provide evidence for biomarker use in initiating antibiotic therapy. In addition, this clinical research evidence was generated within a high-income country, therefore it is unclear if this evidence is generalizable to low-resource settings.

CONCLUSION

In critically ill hospitalized adults with sepsis, there is a significant safe reduction in the total antibiotic days when a daily PCT-guided protocol is administered compared with standard care. A daily CRP-guided protocol does not reduce the total duration of antibiotics.

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AUTHOR CONTRIBUTIONS:

Drs Lall and Hossain have full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Dark, Lall, Perkins, McAuley, Carlson, Clayton, Felton, Gordon, Lone, McCullagh, McMullan, Singer, Stevenson, Walsh, Wilson.

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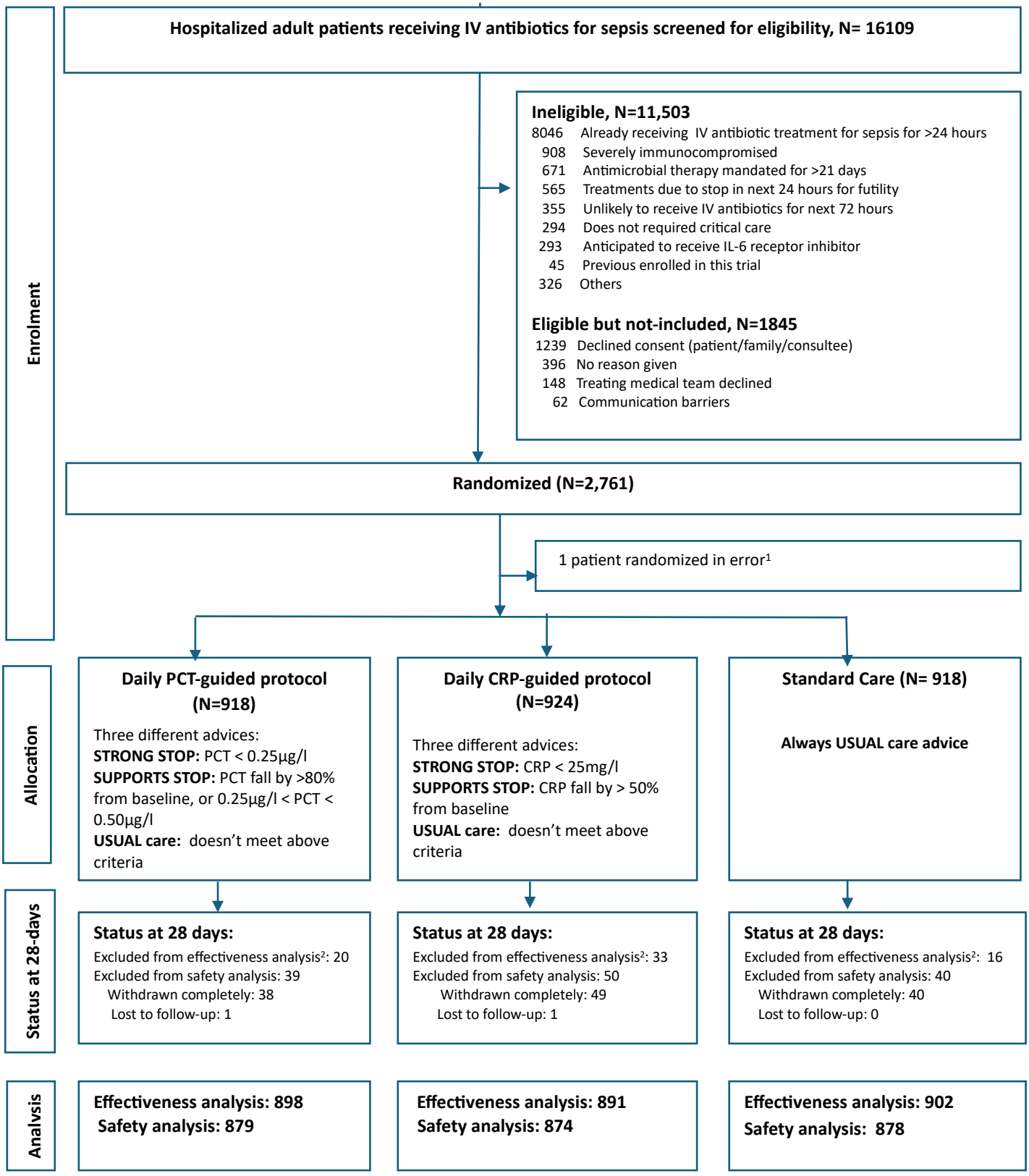
Figure 1: Recruitment, randomization and follow-up in the ADAPT-Sepsis trial.



[1]No data was collected for this patient. [2]11 patients withdrew completely from the trial by day 28 and requested removal of their data. In addition, data were missing and unobtainable from 54 patients.

Table 1: Demographics and clinical characteristics of the randomized patients[1]

Characteristics	**Daily PCT-guided protocol (N=918)**	**Daily CRP-guided protocol (N=924)**	**Standard Care (N=918)**
Age, mean (SD) [N], year	60.6 (15.2) [914]	60.3 (15.6) [918]	59.8 (15.3) [915]
Sex - n (%)			
N	915	918	915
Female	354 (38.7)	366 (39.9)	371 (40.6)
Male	561 (61.3)	552 (60.1)	544 (59.5)
Critical Admission care category - n (%)			
N	908	912	913
Medical	563 (62.0)	558 (61.2)	552 (60.5)
Emergency surgical	245 (27.0)	251 (27.5)	253 (27.7)
Elective surgical	73 (8.0)	73 (8.0)	73 (8.0)
Other	27 (3.0)	30 (3.3)	35 (3.8)
Origin - n (%)			
N	907	911	913
Emergency department	542 (59.8)	525 (57.6)	556 (60.9)
Surgical ward	106 (11.7)	110 (12.1)	97 (10.6)
Medical ward	99 (10.9)	92 (10.1)	83 (9.1)
Operating department	66 (7.3)	78 (8.6)	77 (8.4)
Emergency Assessment Unit (EAU)[2]	21 (2.3)	39 (4.3)	35 (3.8)
Another critical care unit	30 (3.3)	27 (3.0)	28 (3.1)
Other[3]	43 (4.7)	40 (4.4)	37 (4.1)
Place of acquired infection causing sepsis - n (%)			
N	904	904	907
Community acquired	612 (67.7)	616 (68.1)	618 (68.1)

Characteristics	Daily PCT-guided protocol (N=918)	Daily CRP-guided protocol (N=924)	Standard Care (N=918)
Hospital acquired	292 (32.3)	288 (31.9)	289 (31.9)
Presumed site of infection causing sepsis - n (%)[4]			
Respiratory tract	437 (48.3)	447 (49.5)	451 (49.6)
Intra-abdominal	230 (25.5)	208 (23.0)	198 (21.8)
Urinary tract	124 (13.7)	109 (12.1)	118 (13.0)
Unknown focus	98 (10.9)	104 (11.5)	96 (10.6)
Blood stream	84 (9.3)	90 (10.0)	84 (9.3)
Skin and soft tissue	69 (7.6)	73 (8.1)	88 (9.7)
Central nervous system	31 (3.4)	32 (3.5)	20 (2.2)
Ear, nose and throat	19 (2.1)	19 (2.1)	29 (3.2)
Central line related infection	15 (1.7)	9 (1.0)	15 (1.7)
Not categorized	42 (4.7)	45 (5.0)	42 (4.6)
Causative microorganism identified for the infection causing sepsis – n/N (%)	422/901 (46.8)	411/901 (45.6)	428/904 (47.4)
Baseline Core body temperature, mean (SD) [N], °C	37.2 (1.4) [904]	37.2 (1.4) [904]	37.2 (1.4) [906]
Baseline White Cell count, mean (SD) [N], $x10^9$/L	15.7 (9.3) [907]	15.9 (9.8) [909]	15.7 (9.8) [911]
Sepsis Severity – n (%)			
N	915	918	916
Sepsis	465 (50.8)	466 (50.8)	466 (50.9)
Septic Shock	450 (49.2)	452 (49.2)	450 (49.1)
Surgery within last 72 hours – n/N (%)	256/915 (28.0)	258/918 (28.1)	256/916 (28.0)
SOFA score (5 items)[5], median (IQR) [N]	7.0 (5.0, 9.0) [836]	7.0 (5.0, 9.0) [839]	7.0 (5.0, 9.0) [841]
APACHE II[5], mean (SD) [N]	17.5 (6.5) [811]	17.3 (6.4) [825]	17.2 (6.5) [810]

[1]The column percentage sums may not be exactly 100 because of rounding.

Characteristics	Daily PCT-guided protocol (N=918)	Daily CRP-guided protocol (N=924)	Standard Care (N=918)

[2]EAU provides short stay hospital care for up to 72 hours to allow for early assessment and treatment to adult patients, who are referred by their family doctor directly from the community or by an emergency physician from the Emergency Department (ED).
[3]Others includes transfer from another hospital (N=49), hospital ward (N=49), ambulatory care clinic (N=8) and interventional radiology (N=14).
[4]Multiple response per patient, so the sum of column percentages is more than 100.
SD: Standard Deviation, IQR: Interquartile Range.
[5]The Sequential Organ Failure Assessment (SOFA) score ranges from 0 (best) to 20 (worst). The Acute Physiology and Chronic Health Evaluation (APACHE) score ranges from 0 (best) to 71 (worst). The SOFA score assesses organ function failure, and the APACHE II score evaluates disease severity and predicts outcomes in critically ill patients. A SOFA score of 7 and/or APACHE II score of 17 indicates severe organ dysfunction and a high mortality risk, with potential respiratory failure, cardiovascular instability, acute kidney injury, liver dysfunction, altered consciousness, and severe coagulopathy. Patients with these scores require intensive care and close monitoring.

Table 2: Primary and secondary outcomes					
Outcomes	**Daily PCT-guided protocol (N=918)**	**Daily CRP-guided protocol (N=924)**	**Standard Care (N=918)**	**Unadjusted Treatment effect (95% CI), [P-value][1]**	
				Standard care vs. daily PCT-guided protocol	**Standard care vs. daily CRP-guided protocol**
Primary outcomes					
Effectiveness: Total antibiotic treatment duration to 28 days post randomization, mean (SD) [N], days	9.8 (7.2) [898]	10.6 (7.7) [892]	10.7 (7.6) [905]	MD: 0.88 (0.19 to 1.58), [0.01]	MD: 0.09 (-0.60 to 0.79), [0.79]
Safety*:* 28-days all-cause mortality[2], n/N (%)	184/879 (20.9)	184/874 (21.1)	170/878 (19.4)	AD : 1.57 (-2.18 to 5.32), [0.02][3]	AD: 1.69 (-2.07 to 5.45), [0.03][3]
Sensitivity Analysis					
Per protocol analysis for both effectiveness and safety outcomes					
Effectiveness: Total antibiotic treatment duration to 28 days post randomization, mean (SD) [N], days	9.8 (7.2) [880]	10.6 (7.7) [874]	10.7 (7.6) [891]	MD: 0.86 (0.16 to 1.56), [0.02]	MD: 0.05 (- 0.65 to 0.75), [0.88]
Safety*:* 28-days all-cause mortality – n/N (%)	176/860 (20.5)	182/854 (21.3)	166/864 (19.2)	AD: 1.25 (-2.51 to 5.02) [0.02][3]	AD: 2.10 (-1.70 to 5.90) [0.04][3]
CACE Analysis for the effectiveness outcome				MD: 1.00 (0.22 to 1.77), [0.01]	0.10 (-0.70 to 0.91), [0.81]
Imputation analysis, mean (SD) [N]	9.8 (7.3) [915]	10.6 (7.9) [918]	10.8 (7.7) [916]	MD: 0.99 (0.29 to 1.69), [0.005]	MD: 0.15 (-0.55 to 0.85), [0.67]
Pocock's Win Ratio[4]: Using 28-days all-cause mortality status and total antibiotic duration to 28-days post randomization				Odds: 1.12 (1.00 to 1.25), [0.04]	Odds: 0.98 (0.88 to 1.10), [0.77]

Secondary outcomes					
Antibiotic treatment duration for initial sepsis period, mean (SD) [N], days	7.0 (5.7) [893]	7.4 (6.0) [889]	8.1 (6.1) [902]	MD: 1.13 (0.58 to 1.68)	MD: 0.71 (0.16 to1.26)
Antibiotic dose from randomization until 28-days, median (IQR), DDD	11.5 (6.0, 19.1) [797]	12.0 (6.0, 20.1) [773]	11.0 (5.8, 19.8) [760]		
Antibiotic dose for sepsis period, median (IQR)[N], DDD	8.0 (4.0, 14.0) [851]	8.0 (4.2, 15.0) [830]	9.0 (4.8, 17.0) [823]		
Unscheduled care escalation/re-admission					
Number of events	314	349	365	AD: 2.80 (-1.16 to 6.76)	AD: 0.05 (-3.91 to 4.03)
No. of patients with at least one event – n/N (%)	208/888 (23.4)	234/894 (26.2)	236/900 (26.2)	RD: 10.67 (-3.77 to 25.95) OR: 1.16 (0.94 to 1.44)	RD: 0.18 (-14.26 to 15.46) OR: 1.00 (0.81 to 1.24)
Time to first deemed fit for Hospital discharge, mean (SD) [N], days	12.5 (7.9) [190]	13.0 (6.9) [215]	12.4 (7.2) [194]	MD: - 0.09(-1.56 to 1.38)	MD: - 0.59(-2.02 to 0.83)
Time to hospital discharge (survivors), mean (SD) [N], days	12.6 (6.8) [439]	12.6 (6.9) [441]	12.7 (6.8) [436]	MD: 0.10 (-0.81 to 1.01)	MD: 0.11 (-0.80 to 1.02)
Length of ICU stay, median (IQR) [N], days	6.2 (3.1, 12.3) [763]	6.0 (3.1, 11.9) [771]	5.8 (3.0, 12.4) [762]		
Infection relapse/recurrence requiring further antibiotic treatment					
Number of events	15	8	5	AD: -0.66 (-1.51 to 0.01)	AD: -0.003 (-0.85 to 0.67)
No. of patients with at least one event – n/N (%)	11/908 (1.2)	5/908 (0.6)	5/913 (0.5)	RD[5]: -121.2 1 (-565.01 to 101.41)	RD[5]: -0.55 (-444.35 to 222.08)

				OR: 0.45 (0.16 to 1.30)	OR: 0.99 (0.29 to 3.44)
New infection/superinfection at a different anatomical site					
Number of events	41	39	32	AD: -0.57 (-2.13 to 0.93)	AD: -0.34 (-1.90 to 1.15)
No. of patients with at least one event – n/N (%)	29/908 (3.2)	27/908 (3.0)	24/913 (2.6)	RD: -21.50 (-92.76 to 45.02) OR: 0.82 (0.47 to 1.42)	RD: -13.12 (-84.38 to 53.40) OR: 0.88 (0.50 to 1.54)
Suspected clinically relevant antibiotic related events					
Number of events	118	137	118	AD: -0.21 (-2.81 to 2.30)	AD: -0.84 (3.43 to 9.44)
No. of patients with at least one event – n/N (%)	71/888 (8.0)	77/894 (8.6)	70/900 (7.8)	RD: -2.80 (-38.18 to 32.80) OR: 0.97 (0.69 to 1.37)	RD: -10.74 (-46.12 to 24.86) OR: 0.89 (0.64 to 1.25)
90-days all-cause mortality – n/N (%)	217/847 (25.6)	223/846 (26.4)	215/842 (25.5)	AD: -0.09 (-4.29 to 4.08) RD: -0.33 (-17.04 to 16.40) OR: 1.00 (0.80 to 1.24)	AD: -0.82 (-5.03 to 3.34) RD: -3.23 (-19.94 to 13.51) OR: 0.96 (0.77 to 1.19)

SD: Standard Deviation, MD: Mean Difference, AD: Absolute Difference, RD: Relative Difference, OR: Odds Ratio, DDD: Defined Daily Dose.

[1]P-values for primary outcomes analyses only.

[2]For 28-days all-cause mortality, the comparisons are made as Daily PCT-guided protocol vs. Standard care, and Daily CRP-guided protocol vs. Standard care

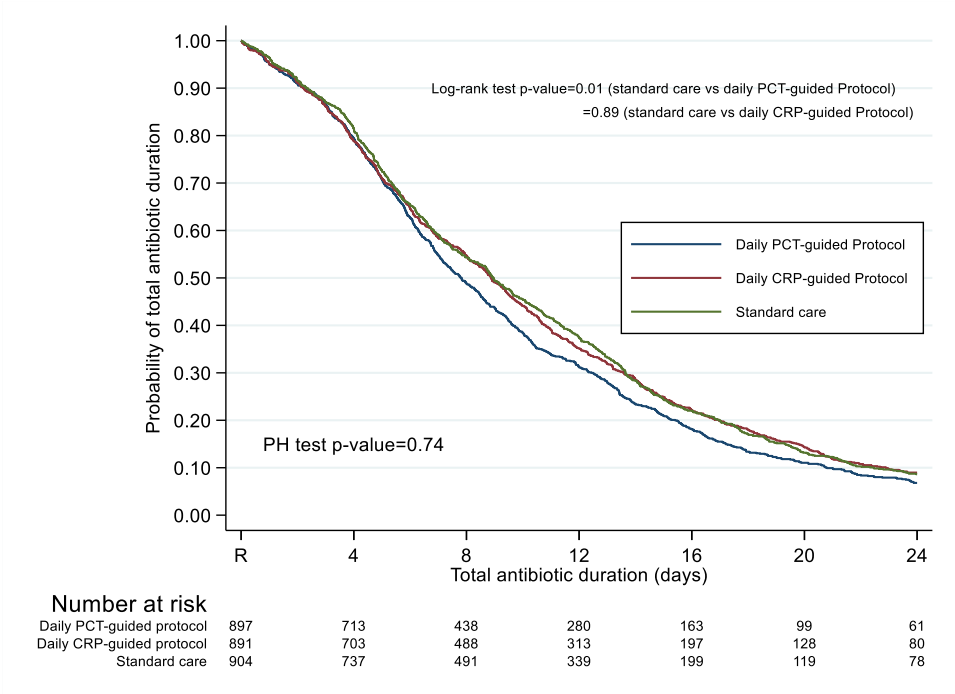
[3]P-values of the test if the RD is less than or equal to the pre-specified margin 5.4% (significance level = 0.025).

[4] The win-ratio is the odds that the intervention treatment wins for any randomly chosen patients' pair (intervention vs control).

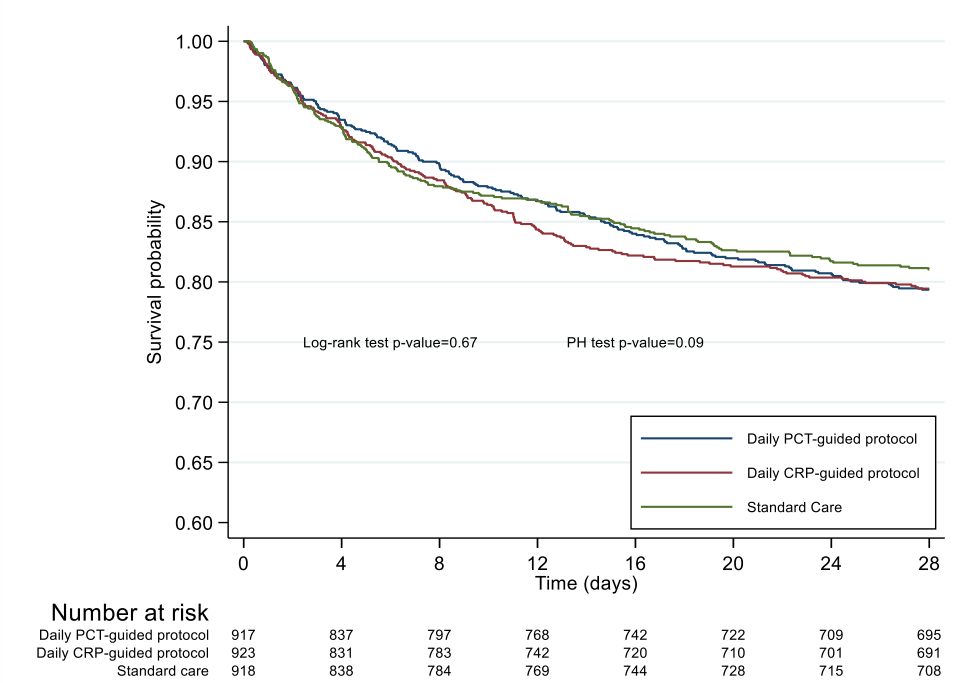
[5]The RD value is very high because the proportions are very small.

Figure 2: Kaplan-Meier curves for (a) probability of total antibiotic duration (primary effectiveness outcome),[1,2] and (b) all-cause mortality up to 28 days (safety outcome)

(a)



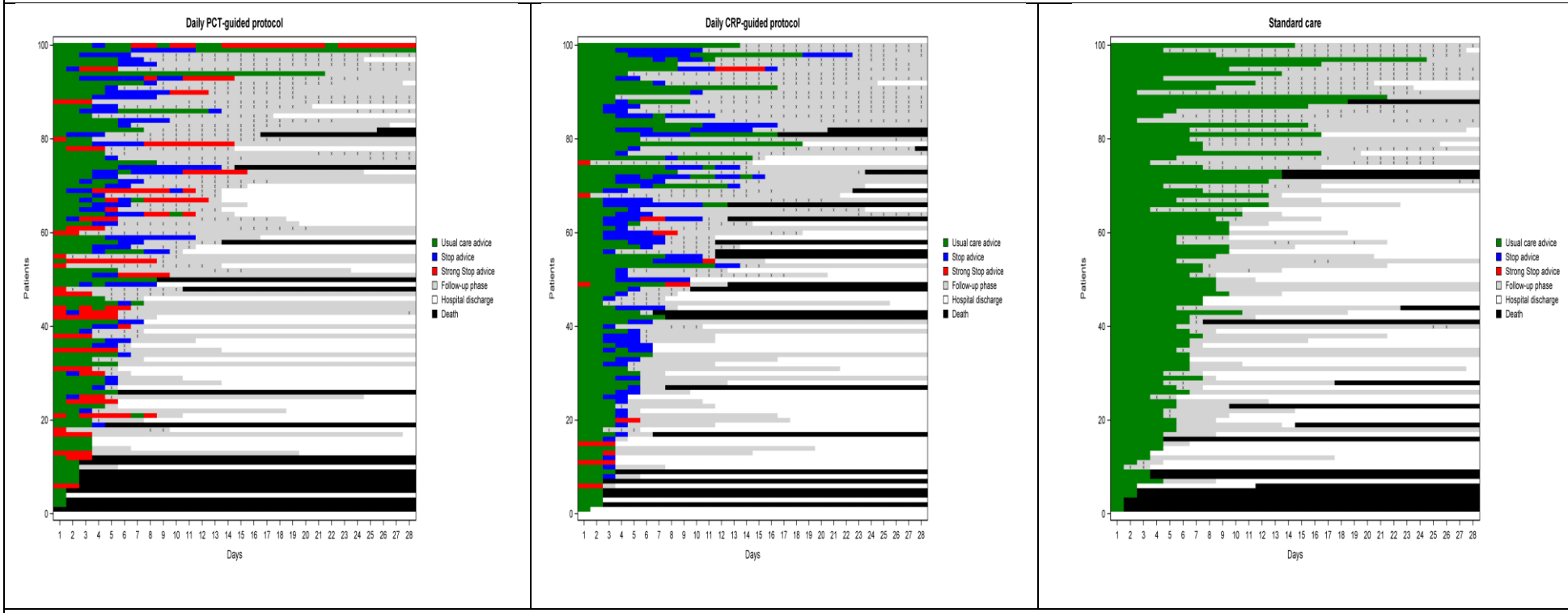
(b)



[1]R=time of randomization.

[2] The median and inter-quartile range (IQR) of the total antibiotic treatment duration up to 28 days for each of the three arms are Daily PCT-guided protocol: 7.8 (4.5, 13.6), Daily CRP-guided protocol: 8.9 (4.5, 14.9), and Standard care: 9.0 (4.7, 14.6).

Figure 3: Indicative maps of patient care pathways



Trial patients were drawn at random (N = 100 per group) and tabulated to indicate their care pathways from randomization to day-28. The trial intervention periods (where patients were receiving antibiotics for sepsis and daily protocolized advice) are indicated by colors (standard care advice (green); stop advice (blue) and strong stop advice (red)). When antibiotics for sepsis are stopped and protocol advice ends, the patient enters the trial follow up phase in hospital (grey) and discharged from hospital (white). Any antibiotics commenced and delivered during follow up are indicated by black crosses. Patients in each group are ordered by length of total antibiotics from randomization to day-28, with the longest duration at the top. Death is indicated in black.

4