Short-course antibiotic therapy for critically ill patients treated for postoperative intra-abdominal infection: the DURAPOP randomised clinical trial

Philippe Montravers, Florence Tubach, Thomas Lescot, Benoit Veber, Marina Esposito-Farèse, Philippe Seguin, Catherine Paugam, Alain Lepape, Claude Meistelman, Joel Cousson, et al.

Short-course antibiotic therapy for critically ill patients treated for postoperative intra-abdominal infection: the DURAPOP randomised clinical trial

Philippe Montravers[1,18*] , Florence Tubach[2], Thomas Lescot[3], Benoit Veber[4], Marina Esposito-Farèse[5], Philippe Seguin[6], Catherine Paugam[7], Alain Lepape[8], Claude Meistelman[9], Joel Cousson[10], Antoine Tesniere[11], Gaetan Plantefeve[12], Gilles Blasco[13], Karim Asehnoune[14], Samir Jaber[15], Sigismond Lasocki[16], Herve Dupont[17] and For the DURAPOP Trial Group

Abstract

Purpose: Shortening the duration of antibiotic therapy (ABT) is a key measure in antimicrobial stewardship. The optimal duration of ABT for treatment of postoperative intra-abdominal infections (PIAI) in critically ill patients is unknown.

Methods: A multicentre prospective randomised trial conducted in 21 French intensive care units (ICU) between May 2011 and February 2015 compared the efficacy and safety of 8-day versus 15-day antibiotic therapy in critically ill patients with PIAI. Among 410 eligible patients (adequate source control and ABT on day 0), 249 patients were randomly assigned on day 8 to either stop ABT immediately (n = 126) or to continue ABT until day 15 (n = 123). The primary endpoint was the number of antibiotic-free days between randomisation (day 8) and day 28. Secondary outcomes were death, ICU and hospital length of stay, emergence of multidrug-resistant (MDR) bacteria and reoperation rate, with 45-day follow-up.

Results: Patients treated for 8 days had a higher median number of antibiotic-free days than those treated for 15 days (15 [6–20] vs 12 [6–13] days, respectively; P < 0.0001) (Wilcoxon rank difference 4.99 days [95% CI 2.99–6.00; P < 0.0001). Equivalence was established in terms of 45-day mortality (rate difference 0.038, 95% CI − 0.013 to 0.061). Treatments did not differ in terms of ICU and hospital length of stay, emergence of MDR bacteria or reoperation rate, while subsequent drainages between day 8 and day 45 were observed following short-course ABT (P = 0.041).

Conclusion: Short-course antibiotic therapy in critically ill ICU patients with PIAI reduces antibiotic exposure. Continuation of treatment until day 15 is not associated with any clinical benefit.

Clinicaltrials.gov identifier: NCT01311765.

---

*Correspondence: philippe.montravers@aphp.fr
[18] Département d'Anesthésie-Réanimation, CHU Bichat Claude Bernard, 48 rue Henri Huchard, 75018 Paris, France
Full author information is available at the end of the article

Introduction

Decreased duration of antibiotic therapy (ABT) is a fundamental antimicrobial stewardship measure [1]. It has recently been suggested that a short course of 4–5 days would be sufficient to cure mild-to-moderate healthcare-associated intra-abdominal infections [2]. However, the results to date are not sufficient to support a similar policy in critically ill patients such as those treated for severe postoperative intra-abdominal infection (PIAI), who require supportive care for organ dysfunctions, and those with high proportions of multidrug-resistant (MDR) bacteria [3–8].

In single-centre, retrospective, epidemiological studies analysing these ICU patients, the duration of ABT ranged between 7 and 15 days [9–11]. In addition, a significant increase in the duration of ABT was reported when MDR bacteria were cultured [10, 11]. The existing guidelines provide no relevant recommendations and suggest that the decision-making process should be based on clinician judgement and laboratory results [4, 7, 8].

We therefore conducted a randomised trial to compare 8-day and 15-day ABT regimens in a well-defined group of critically ill patients with PIAI, as confirmed by surgery and peritoneal specimen culture results.

Materials and methods

Study design and organisation

This multicentre, prospective, controlled, randomised, open-label trial was conducted in 21 French intensive care units (ICU) (Fig. 1 and electronic supplementary material [ESM] Figure-S1) between May 2011 and February 2015. The study was approved by the appropriate ethics committee (CPP Ile-de-France-I 2010-08-12392). Written informed consent was obtained from the patients or their legal representatives before study inclusion. In the event of impaired decision-making capacity without a legal representative available, the patient's informed consent could be obtained after enrolment (emergency inclusion).

Study population

Patients were eligible for enrolment in the study if the following conditions were fulfilled: (1) admission to the ICU; (2) elapse of less than 24 h since surgery for PIAI (i.e. ≤ 60 days following an interventional procedure or any surgery performed in the peritoneal or retroperitoneal space showi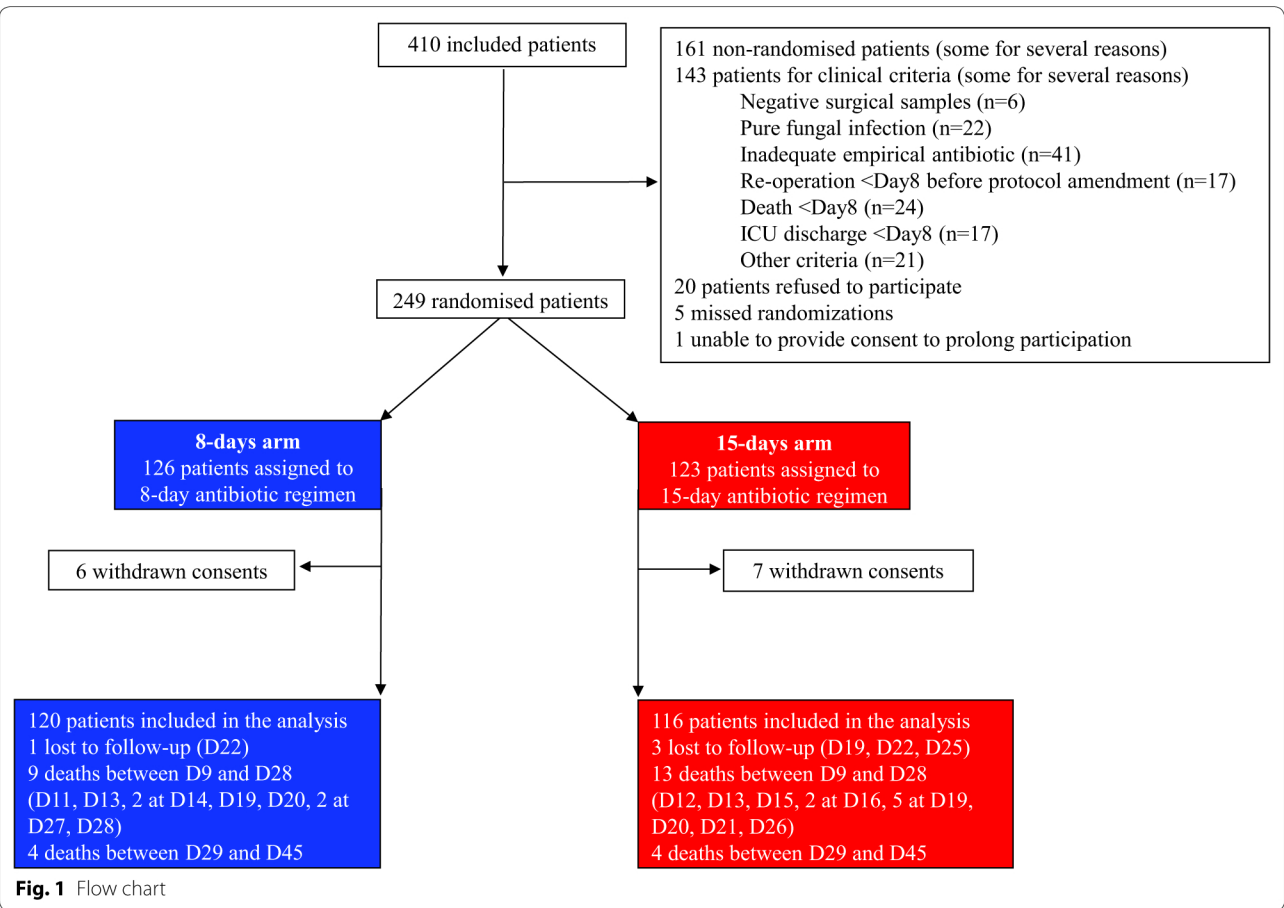ng gross pus or purulent effusion in the peritoneal cavity, or several collections); (3) adequate source control; (4) operative samples yielding positive microbiological cultures; (5) empirical ABT initiated within 24 h after completion of surgery; (6) written informed consent or emergency inclusion. The criteria for ineligibility are presented in the Methods-ESM.

Randomisation

Patients were included at day 0 (day of source control procedure). Randomisation was performed on day 8 to avoid any divergence between the arms before the two treatment strategies began to differ (Methods-ESM). Patients were randomly assigned on day 8, in a one/one ratio, to either cessation of ABT on day 8 (8-day arm) or continuation of antibiotics for another 7 days (15-day arm). The randomisation list was computer-generated, balanced by blocks of variables, of undisclosed size and stratified by centre. Allocation concealment was achieved using a centralised, secure, interactive web-response system accessible from each study centre (Cleanweb, Telemedicine Technologies S.A.S, Boulogne-Billancourt, France). Investigator blinding to arm assignment was not practicable, but all investigators were unaware of aggregate outcomes during the study.

Antibiotic treatments

Empirical ABT was recommended according to the French Guidelines for PIAI (Methods-ESM) [5]. However, ABT and management were left to the discretion of the attending physicians, including drug plasma monitoring and any adaptation considered necessary. Investigators were invited to convert the empirical regimen into narrow-spectrum treatment, based on culture results obtained within 48–72 h after surgery. It was planned to withdraw antibiotics at the end of allocated treatment. However, the physician in charge of the patient was the final arbiter of the decision when to stop ABT. If the physician did not follow the randomisation assignment, the reason for deviation was recorded. The use of procalcitonin to guide treatment decision making was left to the attending physician's discretion.

This multicentre prospective randomised study evaluated the efficacy and safety of an 8-day course of antibiotic therapy in ICU patients treated for postoperative intra-abdominal infections. This regimen substantially reduced antibiotic exposure and no clinical benefit was observed when treatment was extended to 15 days.

Fig. 1 Flow chart

Flow chart content:

410 included patients

161 non-randomised patients (some for several reasons)
143 patients for clinical criteria (some for several reasons)
  Negative surgical samples (n=6)
  Pure fungal infection (n=22)
  Inadequate empirical antibiotic (n=41)
  Re-operation <Day8 before protocol amendment (n=17)
  Death <Day8 (n=24)
  ICU discharge <Day8 (n=17)
  Other criteria (n=21)
20 patients refused to participate
5 missed randomizations
1 unable to provide consent to prolong participation

249 randomised patients

8-days arm
126 patients assigned to 8-day antibiotic regimen

15-days arm
123 patients assigned to 15-day antibiotic regimen

6 withdrawn consents

7 withdrawn consents

120 patients included in the analysis
1 lost to follow-up (D22)
9 deaths between D9 and D28 (D11, D13, 2 at D14, D19, D20, 2 at D27, D28)
4 deaths between D29 and D45

116 patients included in the analysis
3 lost to follow-up (D19, D22, D25)
13 deaths between D9 and D28 (D12, D13, D15, 2 at D16, 5 at D19, D20, D21, D26)
4 deaths between D29 and D45

Data collection

The following criteria were recorded from day 8 until day 45: death; time to discharge from ICU and hospital; need for reoperation or percutaneous drainage for any reason; need for another course of ABT for any reason; bacteraemia; microbiological recurrence in peritoneal samples, defined as culture of at least one of the initial causative micro-organisms from samples obtained from reoperation or percutaneous drainage (otherwise it was considered to be a superinfection). MDR bacteria were defined according to expert recommendations (Methods-ESM) [12]. Emergence of MDR bacteria in surveillance samples was assessed on a weekly basis from ICU admission to discharge. Organ failure (according to the SOFA score [13]) was evaluated on day 15 and day 28 in survivors not discharged from hospital.

Outcome measures

Recruitment difficulties led to a switch from two primary endpoints to one (Methods-ESM). The primary endpoint was the number of antibiotic-free days (i.e. number of days alive and antibiotic-free) from day 8 to day 28 (analysis of superiority); patients who died before day 28 were counted as no antibiotic-free days.

The key secondary endpoints were equivalence in terms of 45-day mortality and superiority analyses of death from any cause at day 28. Other secondary outcomes were: length of ICU and hospital stay; need for reoperation for any reason; need for additional drainage; superinfection or recurrent infection, assessed by microbiological sample; and another course of ABT for any reason.

Clinical failure was defined as the presence of any of these criteria between day 8 and day 45. Microbiological failure was defined as the presence of bacteria cultured from blood, pus or fluid collected from the abdominal cavity or abscesses collected from reoperation, or percutaneous drainage, infection recurrence or superinfection ≥ 48 h after stopping adequate ABT, or emergence of MDR micro-organisms in clinical isolates and surveillance samples assessed between day 1 and discharge from the ICU. The organ failure-free survival rate according to SOFA score was determined on day 15 and day 28.

Predefined subgroups of interest were: patients > 80 years; morbidly obese patients (BMI > 35 kg/m^2);

severe infection with SAPS II score > 40; [14] patients with bacteraemia during the first 3 days before and after the initial operation; patients with peritoneal samples yielding *Pseudomonas aeruginosa* or enterococci.

In post hoc analyses, evaluation of both strategies from the pragmatic point of view by incorporating the actual duration of antibiotic use was made using the concepts of desirability of outcome ranking (DOOR) and response adjusted for duration of antibiotic analyses (RADAR) [15]. Patients were divided into five mutually exclusive categories according to the postoperative course: (1) recovery without any complication; (2) recovery with additional ABT; (3) recovery with additional percutaneous drainage; (4) recovery with additional abdominal procedure; and (5) death. Probabilities of a better desirable outcome for a randomly selected patient, based on adjusted ranks (RADAR), were calculated for the two strategies.

Statistical analysis

The trial was designed to determine whether the 8-day antibiotic regimen was superior in terms of antibiotic use, assessed by the number of antibiotic-free days. Assuming 11.5 ± 5.5 (mean $\pm$ SD) antibiotic-free days for the 15-day arm (unpublished data from the Prorata trial, in the subgroup of patients with PIAI) [16], 122 patients/arm would provide 90% power at a two-sided α risk of 0.05 to detect a 20% (2.3 days) increase of the number of antibiotic-free days. We therefore planned to include and randomise 244 patients.

Categorical variables are reported as numbers (%). Continuous variables are expressed as mean $\pm$ SD and median [interquartile range (IQR)]. For all analyses (R software version 3.1), the significance alpha level was 0.05.

The primary endpoint was analysed according to the intention-to-treat (ITT) principle. The absolute difference between arms in terms of the numbers of antibiotic-free days was assessed using the two-sided Wilcoxon rank sum test. The center effect was evaluated in statistical analyses as a fixed effect for the principal and secondary outcomes. Multiple imputation methods (MICE) were used on missing values [17].

The equivalence in terms of 45-day mortality was analysed in the ITT population and repeated in the per-protocol population (defined as duration of treatment according to randomisation arm [$\pm$ 1 day] and 48 h of washout before taking new antimicrobials). Equivalence was assessed by the 95% CI ($\pm$ 10%) of the difference of the 45-day mortality rates. Overall survival was estimated using Kaplan–Meier methods and the log-rank test. All other secondary analyses were performed in the ITT

population using Student's *t* test and Fisher's or Wilcoxon's test as appropriate.

Linear and logistic regressions (exploratory analyses) were fitted in order to test the interaction of predefined subgroups of interest and the randomisation arm when explaining the following outcomes: antibiotic-free days, 45-day mortality and the emergence of MDR bacteria.

Results

Patient characteristics

Overall, 410 patients were included in the study and 249 patients were randomised on day 8 following surgery. After withdrawal of consent for 13 patients, data for 236 patients were analysed. The clinical and therapeutic characteristics at admission for PIAI are presented in Table 1 (ESM-Table-S1). Twenty-eight patients (14 patients in each arm) who underwent reoperation between day 0 and day 8 at a mean of 4 [2–6.5] days after inclusion were also included (Fig. 1). This group did not differ statistically significantly from the other randomised patients (ESM-Table-S2).

Fifty-six positive blood cultures were reported in 37 patients in the 3 days before and after inclusion. Overall, 591 micro-organisms were cultured from peritoneal samples (ESM-Table-S3). Empirical ABT was started on day 0 for PIAI in all patients, followed by a definitive antibiotic regimen based on microbiological results and susceptibility testing (ESM-Table-S4 and S5).

At day 8, 67 (26.9%) patients still had a SOFA score $\geq$ 3, and 72 (28.9%) patients had resumed oral feeding. The clinical characteristics at day 8 were similar in both arms except for a higher proportion of patients receiving mechanical ventilation in the 8-day arm (40/120 [35%] vs 24/116 [21%], p = 0.023) (Table 1 and ESM-Table-S6).

The allocated duration of ABT was followed in 92 (79%) patients in the 8-day arm and 95 (82%) patients in the 15-day arm (ESM-Results). Overall, 77 patients in the 8-day arm and 66 patients in the 15-day arm were included in the per-protocol analysis (ESM-Figure-S2).

Primary outcome

The number of antibiotic-free days between day 8 and day 28 was higher in the 8-day arm (median [IQR] 15 [6–20] days) than in the 15-day arm (12 [6–13] days) (difference in location estimates 4.99 days, 95% CI [2.99–6.00], p = 9.63×10^{-5}) (Fig. 2 and ESM-Figure-S3).

Secondary outcomes

The 45-day mortality rates in the ITT population did not differ between the two arms (difference 3.8%, 95% CI [1.2–6.2]) (Table 2). The analysis was repeated in the per-protocol population: the 45-day mortality rates were 7/77

Table 1 Demographic and clinical characteristics and antibiotic regimens of the study patients according to treatment arm

Variable	Missing data Control/experimental arms	15-day arm (n = 116)	8-day arm (n = 120)
Characteristics on the day of enrolment (Day 0)			
Age, years, median [IQR]	0/0	66·5 [59–77]	66 [57–76]
Patients aged > 80 years, n (%)	0/0	18 (16)	12 (10)
Male sex, n (%)	0/0	70 (60)	82 (68)
No underlying disease, n (%)	0/1	60 (52)	72 (61)
Charlson score, median [IQR]	0/0	5 [3–7]	4 [2–7]
Body mass index, kg/m^2, median [IQR]	9/10	27.3 [23–31.6]	28.1 [24–33]
Body mass index > 35 kg/m^2, n (%)	9/10	16 (15)	20 (18)
SAPS II score, median [IQR]	10/6	45 [34–51.8]	44.5 [35–56.8]
SAPS II score > 40, n (%)	10/6	63 (59)	73 (64)
SOFA score, median [IQR]	16/11	6 [3–8]	7 [4–9]
Mechanical ventilation, n (%)	16/11	83 (74)	96 (84)
Vasoactive agents, n (%)	16/11	79 (71)	78 (68)
Sedation, n (%)	16/11	77 (71)	91 (81)
Renal replacement therapy, n (%)	16/11	11 (10)	13 (11)
Source of contamination, n (%)			
Colon or rectum, n (%)	0/0	49 (42)	57 (48)
Small bowel, n (%)	0/0	37 (32)	39 (32)
Gastroduodenal, n (%)	0/0	15 (13)	13 (11)
Perforation, n (%)	0/1	61 (53)	53 (45)
Ischaemia/bowel necrosis, n (%)	0/1	17 (15)	19 (16)
Abscess, n (%)	0/1	23 (20)	17 (14)
Source control procedure, n (%)			
Percutaneous drainage, n (%)	0/2	1 (1)	5 (6)
Resection/excision, n (%)	0/2	66 (57)	74 (63)
Ostomy, n (%)	0/1	71 (61)	70 (59)
Anastomosis, n (%)	0/3	15 (13)	20 (17)
Patch/suture, n (%)	0/3	32 (28)	41 (35)
Intraoperative drainage, n (%)	0/2	95 (82)	87 (74)
Bypass/derivation, n (%)	0/3	6 (5)	2 (2)
Evaluation of source control at the end of surgery			
Total source control, n (%)	27/30	72 (81)	76 (84)
Minimal residual source of contamination, n (%)	27/30	9 (10)	9 (10)
Absence of macroscopic residual contamination, n (%)	27/30	66 (80)	70 (82)
Minimal residual contamination, n (%)	27/30	6 (7)	11 (13)
Most frequently isolated pathogens from surgical samples[a]			
Enterobacteriaceae, n (%)[b]	3/1	115 (37)	102 (36)
Enterococci, n (%)[b]	3/1	60 (19)	61(22)
Anaerobes, n (%)[b]	3/1	42 (14)	43 (15)
Most frequently isolated MDR pathogens from surgical samples[a]			
ESBL producing *Enterobacteriaceae*, n (%)[b]	12/12	17/40 (42)	22/37 (59)
AmpC-hyperproducing *Enterobacteriaceae*, n (%)[b]	12/12	18/38 (47)	15/33 (45)
Empirical antibiotic regimens initiated on surgery			
Combination therapy, n (%)	0/0	107 (92)	111 (92)
Piperacillin/tazobactam, n (%)	0/0	71 (61)	74 (62)
Glycopeptides, n (%)	0/0	42 (36)	53 (44)
Aminoglycosides, n (%)	0/0	70 (60)	85 (71)

Table 1 continued

Variable	Missing data Control/experimental arms	15-day arm (n = 116)	8-day arm (n = 120)
Characteristics on the day of randomisation (Day 8)			
SOFA score, median [IQR]	18/21	1 [0–3]	2 [0–5]
Mechanical ventilation, n (%)	3/5	24 (21)	40 (35)
Vasoactive agents, n (%)	3/5	10 (9)	12 (10)
Sedation, n (%)	4/5	15 (13)	15 (13)
Renal replacement therapy, n (%)	3/5	6 (5)	12 (10)
Parenteral nutrition, n (%)	14/15	56 (55)	54 (51)
Enteral nutrition, n (%)	4/6	36 (32)	46 (40)
Oral nutrition, n (%)	4/5	35 (31)	37 (32)

IQR interquartile range, *SAPS II* Simplified Acute Physiology Score II, *SOFA* sepsis-related Organ Failure Assessment

a Postoperative intra-abdominal infection documented microbiologically on surgical samples at the time of enrollment

b Results are expressed as number of organisms and proportions

Table 2 Emergence of multidrug-resistant microorganisms and fungi assessed between Day 1 and discharge from ICU

Variable	Missing data Control/experimental arms	15-day arm (n = 116)	8-day arm (n = 120)
MDR bacteria cultured in surveillance samples			
Number of patients with positive samples, n (%)	12/13	23/104 (22)	20/107 (19)
Methicillin-resistant *Staphylococcus aureus*, n (%)	12/13	2/22 (9)	4/20 (20)
ESBL-producing *Enterobacteriaceae*, n (%)	12/13	18/23 (78)	13/20 (65)
AmpC-hyperproducing *Enterobacteriaceae*, n (%)	12/13	3/22 (14)	2/20 (10)
A. baumanii and *S. maltophilia*, n (%)	12/13	1/22 (5)	2/20 (10)
Pseudomonas aeruginosa, n (%)	12/13	1/22 (5)	1/20 (5)
MDR bacteria in clinical isolates			
Number of patients with positive samples, n (%)	12/12	40/104 (38)	38/108 (35)
Methicillin-resistant *Staphylococcus aureus*, (%)	12/12	10/38 (26)	5/34 (15)
ESBL producing *Enterobacteriaceae*, n (%)	12/12	17/40 (42)	22/37 (59)
AmpC-hyperproducing *Enterobacteriaceae*, n (%)	12/12	18/38 (47)	15/33 (45)
A. baumanii and *S. maltophilia*, n (%)	12/12	5/38 (13)	4/34 (12)
Pseudomonas aeruginosa, n (%)	12/12	5/38 (13)	5/33 (15)
Emergence of fungi, n (%)			
Number of patients with positive samples, n (%)	10/13	27/106 (25)	22/107 (21)
Candida albicans, (%)	10/13	16/32 (50)	19/28 (68)
Non-albicans *Candida* spp., n (%)	10/13	12/32 (38)	9/28 (32)
Candida glabrata, n (%)	10/13	7/32 (22)	3/28 (11)

Results are expressed as number of positive results among the samples

A. baumanii, Acinetobacter baumannii, S. maltophilia: Stenotrophomonas maltophilia, ESBL extended–spectrum betalactamase-producing *Enterobacteriaceae*

(9.1%) in the 8-day arm and 9/66 (13.6%) in the 15-day arm (difference 4.5%, 95% CI [1.13–7.96]).

Mortality rates from day 8 to day 28 in the ITT population were 9/120 (7.5%) in the 8-day arm and 13/116 (11.2%) in the 15-day arm (p = 0.37; OR 0.64 [in favour of the 8-day arm] 95% CI [0.23–1.7]). Similar results were observed in the PP population.

At day 28, the probability that the RADAR score would have been better with the 8-day regimen was 49.65% (95% CI [48.82–50.48]).

The log-rank test (p = 0.327) and Kaplan–Meier survival curves (Fig. 3) from randomisation until day 45 did not show any significant difference in terms of survival times between the two arms. Kaplan–Meier survival
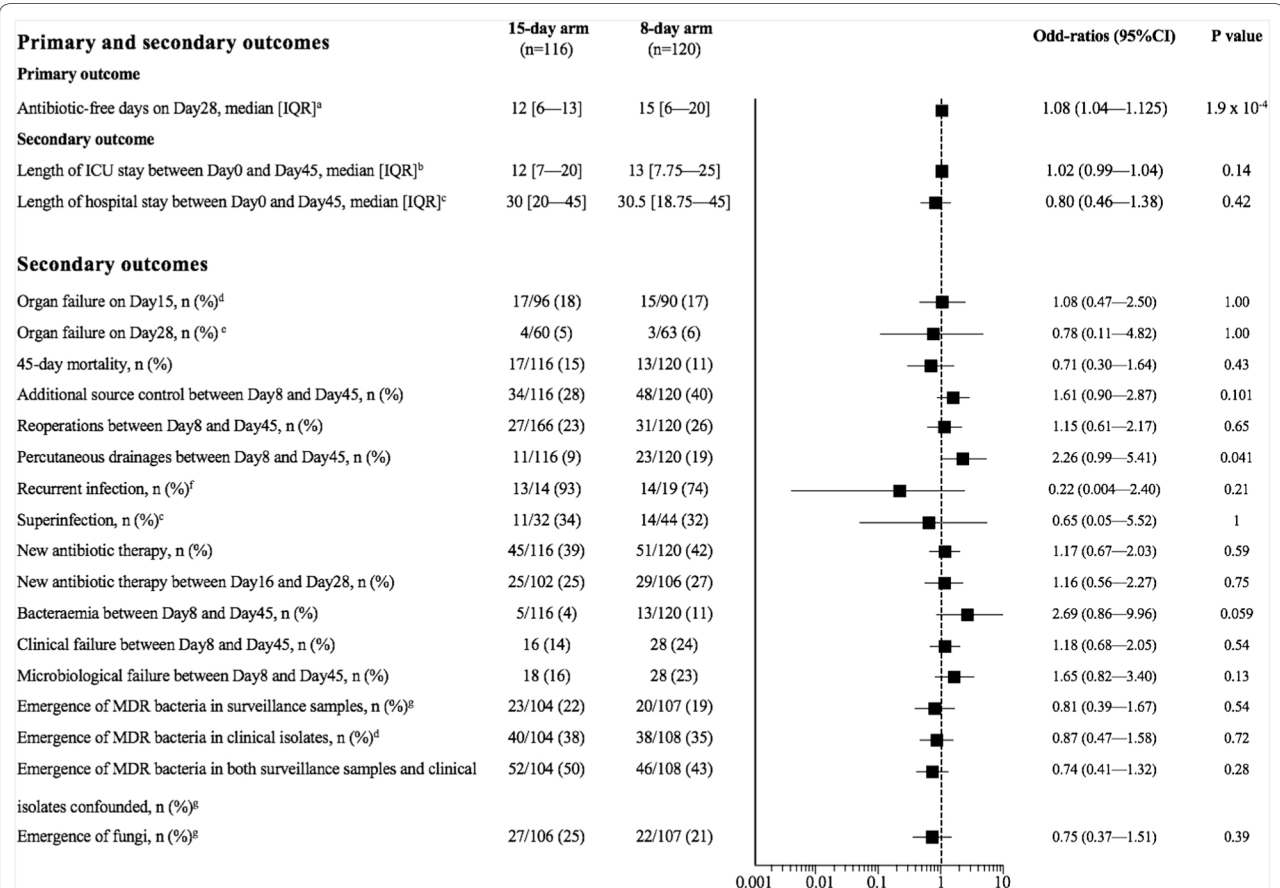
Primary and secondary outcomes	15-day arm (n=116)	8-day arm (n=120)	Odd-ratios (95%CI)	P value
Primary outcome				
Antibiotic-free days on Day28, median [IQR][a]	12 [6—13]	15 [6—20]	1.08 (1.04—1.125)	1.9×10^{-4}
Secondary outcome				
Length of ICU stay between Day0 and Day45, median [IQR][b]	12 [7—20]	13 [7.75—25]	1.02 (0.99—1.04)	0.14
Length of hospital stay between Day0 and Day45, median [IQR][c]	30 [20—45]	30.5 [18.75—45]	0.80 (0.46—1.38)	0.42
Secondary outcomes				
Organ failure on Day15, n (%)[d]	17/96 (18)	15/90 (17)	1.08 (0.47—2.50)	1.00
Organ failure on Day28, n (%)[e]	4/60 (5)	3/63 (6)	0.78 (0.11—4.82)	1.00
45-day mortality, n (%)	17/116 (15)	13/120 (11)	0.71 (0.30—1.64)	0.43
Additional source control between Day8 and Day45, n (%)	34/116 (28)	48/120 (40)	1.61 (0.90—2.87)	0.101
Reoperations between Day8 and Day45, n (%)	27/166 (23)	31/120 (26)	1.15 (0.61—2.17)	0.65
Percutaneous drainages between Day8 and Day45, n (%)	11/116 (9)	23/120 (19)	2.26 (0.99—5.41)	0.041
Recurrent infection, n (%)[f]	13/14 (93)	14/19 (74)	0.22 (0.004—2.40)	0.21
Superinfection, n (%)[c]	11/32 (34)	14/44 (32)	0.65 (0.05—5.52)	1
New antibiotic therapy, n (%)	45/116 (39)	51/120 (42)	1.17 (0.67—2.03)	0.59
New antibiotic therapy between Day16 and Day28, n (%)	25/102 (25)	29/106 (27)	1.16 (0.56—2.27)	0.75
Bacteraemia between Day8 and Day45, n (%)	5/116 (4)	13/120 (11)	2.69 (0.86—9.96)	0.059
Clinical failure between Day8 and Day45, n (%)	16 (14)	28 (24)	1.18 (0.68—2.05)	0.54
Microbiological failure between Day8 and Day45, n (%)	18 (16)	28 (23)	1.65 (0.82—3.40)	0.13
Emergence of MDR bacteria in surveillance samples, n (%)[g]	23/104 (22)	20/107 (19)	0.81 (0.39—1.67)	0.54
Emergence of MDR bacteria in clinical isolates, n (%)[d]	40/104 (38)	38/108 (35)	0.87 (0.47—1.58)	0.72
Emergence of MDR bacteria in both surveillance samples and clinical isolates confounded, n (%)[g]	52/104 (50)	46/108 (43)	0.74 (0.41—1.32)	0.28
Emergence of fungi, n (%)[g]	27/106 (25)	22/107 (21)	0.75 (0.37—1.51)	0.39

Fig. 2 Primary and secondary outcomes (two-sided analyses on ITT population). [a]Deceased patients have 0 days free of antibiotics; [b]deceased patients leave the ICU on the day of death; [c]deceased patients leave the hospital on the day of death; [d]among patients still hospitalised at day 15; [e]among patients still hospitalised at day 28; [f]among those who underwent reoperation or additional drainage; [g]among those who underwent surveillance samples or additional clinical isolates. Clinical and microbiological failures: see definitions in "Materials and methods". IQR interquartile range, ICU intensive care unit, MDR bacteria multidrug-resistant bacteria

probability estimates at day 45 were about 0.89 for the 8-day arm and 0.85 for the 15-day arm.

No significant difference between the arms was observed for emergence of MDR bacteria (Table 2).

Thirty-three patients in the 15-day arm and 40 patients in the 8-day arm were still hospitalised at day 45, and 16 patients (eight in each arm) were still in ICU. Other secondary outcomes are presented in Fig. 2.

Outcomes in predefined subgroups of interest

In order to evaluate differences of treatment effects in terms of antibiotic-free days, 45-day mortality and emergence of MDR bacteria in predefined specific subgroups of patients (ESM-Table 7), regressions were fitted and the interactions of each subgroup and the randomisation arm were tested (ESM-Tables 8a-8r).

Linear regression showed a significant association between antibiotic-free days and the interaction between randomisation arm and enterococcal infections
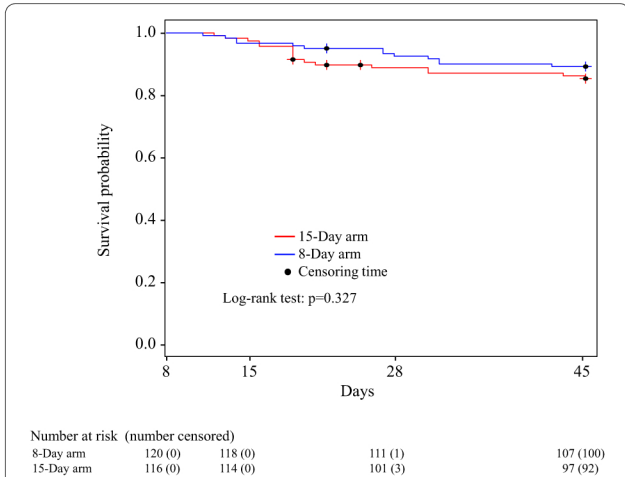

Fig. 3 Kaplan-Meier curves of the probability of survival from randomisation to day 45 according to treatment arm

(ESM-Table 8e) (estimate 4.26, 95% CI [1.07–7.46], p = 0.0092), showing a significantly higher mean ± SD number of antibiotic-free days in the group of patients with enterococcal infections (n = 106), (13.9 ± 5.5 vs 7.9 ± 6.3 days for the 8-day and 15-day arms, respectively).

Another association (but with a low level of evidence) was identified by logistic regression, namely that between the emergence of MDR bacteria and the interaction between randomisation arm and *Pseudomonas* infections (ESM-Table 8r: OR 0.20, 95% CI [0.039–0.99], p = 0.0491). In the group of patients with *Pseudomonas* infection, emergence of MDR bacteria was observed in 10/17 (59%) patients in the 15-day arm versus 4/19 (21%) in the 8-day arm.

Discussion

In this cohort of ICU patients with PIAI, in whom microbiological criteria were applied to diagnose intra-abdominal infection and who received appropriate initial empirical ABT, an 8-day antibiotic regimen reduced antibiotic exposure with equivalence in terms of 45-day mortality rates and no statistically significant difference in terms of 28-day mortality rate or clinical and bacteriological outcomes. The number of antibiotic-free days between day 8 (randomisation) and day 28 was higher in the 8-day arm, with an absolute difference of 3 days, corresponding to a 15% relative reduction in antibiotic exposure. No significant differences were observed for other outcomes, including mortality rate, infection recurrence, new ABT, and length of ICU and hospital stay.

The optimal duration of ABT for complicated intra-abdominal infections has been extensively debated, but data are lacking in ICU patients. Recent randomised trials evaluating new antibiotic agents for mild-to-moderate intra-abdominal infections have studied shortened durations of therapy [18–21], but limited numbers of cases of PIAI were included. Short-course treatments have been shown to be as effective as longer-course treatments for community-acquired peritonitis [2] and appendicitis [22], but not for PIAI in ICU patients. The 8-day course was chosen on the basis of the literature available at the time the protocol was designed. With growing confidence in less prolonged treatment, short-course therapy could be proposed in low-severity ICU cases. However, the need for additional drainage and bacteremia between day-8 and day-45 observed in the short-treatment arm could be considered to indicate a slightly higher failure rate of this regimen.

Our study population is representative of the ICU patients treated for PIAI [23–25]. The high proportion of exclusions before randomisation illustrates the uncertainties of management of these high-risk cases, including inadequacy of empirical ABT and premature death, with consequent recruitment difficulties. The proportion of inadequate empirical therapies in PIAI patients ranges between 10 and 90% [9, 11, 26], which justifies the recommendations for broad-spectrum ABT to target most of the potential micro-organisms [3–8]. Reoperation is common, performed in 15–51% of cases [9, 11, 26]. In addition, the early mortality rate can reach 70% in the first 10 days post surgery in patients with septic shock [27].

In our study, complication rates were similar in the two arms, with additional source control required in one-third of all patients. Surprisingly, there was a higher rate of percutaneous drainage in the 8-day arm. The attending physicians may have tended to screen for superinfection or recurrence more frequently in case of doubt when antibiotic administration was stopped early. Reoperation rates during the postoperative course of PIAI usually range between 5 and 51% of cases [9, 11, 26, 28]. The need for additional drainage is reported in 14–20% of patients [26].

Shortening the duration of ABT might help to contain the emergence of MDR bacteria in ICU patients [1, 29]. Surprisingly, we did not detect any between-group difference for the rates of emergence of MDR bacteria in the 15-day arm except for *Pseudomonas aeruginosa*, corresponding with previous reports from retrospective single-centre studies [24, 30]. However, the calculated sample size was not designed to assess this effect. Similarly, we did not observe any difference in the length of ICU stay between the two arms. However, length of stay depends on many factors not directly related to duration of ABT.

Several limitations need to be considered when interpreting our results. Firstly, the primary endpoint was not truly patient-centred in this high-risk population and was closely related to the intervention, almost directly determined by the study design. This criterion was previously used by Chastre et al. in their pivotal study assessing duration of ABT in ventilator-associated pneumonia [31]. In view of the extreme severity of illness in the study population, superiority in terms of the number of antibiotic-free days can be difficult to establish. Complications in this high-risk population could have increased the relapse rate or caused additional morbidity in the 8-day arm. Secondly, this study is underpowered to evaluate any clinically important effect on mortality. Recruitment difficulties due to strict randomisation criteria led to a switch from two primary endpoints to one, with a concern for interpreting the outcome results at 45-day. The unblinded design of our study could also be open to criticism. Allocation of the duration of ABT was delayed to day 8 to standardise patient follow-up, using rigorous

criteria for outcome evaluation. Repeated monitoring of plasma antibiotic levels as well as various antibiotic administration regimens would have been difficult to perform under blinded conditions. Moreover, a double-blind design would have influenced the length of hospital stay for patients in the 15-day arm due to placebo infusion. A large subset of patients was excluded before randomisation, as indicated on the flow chart. Delayed randomisation at day 8, when the strategies in the two arms began to differ, allowed exclusion of cases with a high initial mortality rate, inadequacy of empirical ABT, and early reoperation. This important choice was made to avoid any focus on patients in whom no ABT strategy would have helped and the bias induced by their high mortality rate. This selection also explains the lower mortality rates observed in our study population. No centre effects were found in the statistical analysis. However, the strong differences in the number of recruited patients per centre might have induced bias results. Finally, no conclusions can be drawn concerning neutropenic or immunosuppressed patients, patients with recurrent intra-abdominal infection or patients with fungal infections.

In summary, an 8-day antibiotic regimen substantially reduced antibiotic exposure for ICU patients who develop microbiologically proven PIAI, while continuation of ABT from 8 to 15 days did not provide any clinical benefit. The issues of a higher number of cases of subsequent drainages and increased bacteremia following short-course ABT requires clarification. The lack of effect of the 8-day regimen on the emergence of MDR bacteria is another surprising finding that deserves attention. The clinical characteristics and causes of PIAI among patients in our cohort and the consistency of the results suggest that our conclusions may be applicable to many ICU patients with PIAI. This type of approach could help to reduce antibiotic use.

Author details
[1] Anaesthesiology and Critical Care Medicine, Bichat-Claude Bernard University Hospital, HUPNSV, AP-HP, INSERM, UMR 1152, Paris Diderot Sorbonne Cite University, Paris, France. [2] Département de Biostatistique, Santé Publique et Information Médicale (BIOSPIM), Hôpital Pitié-Salpêtrière, AP-HP, INSERM, UMR 1123, ECEVE, CIC-EC 1425, Sorbonne Universités, UPMC Univ Paris 06, 75013 Paris, France. [3] Department of Anaesthesiology and Critical Care Medicine, St Antoine Hospital, APHP, Sorbonne Universites, UPMC Univ Paris 06, Paris, France. [4] Pole Anesthésie-Réanimation-SAMU, Rouen University Hospital, Rouen, France. [5] INSERM CIC-EC 1425, Unité de Recherche Clinique, HUPNVS, CHU Bichat-Claude Bernard, APHP, Paris, France. [6] Department of Anaesthesiology and Surgical Intensive Care Medicine, CHU Rennes, Rennes, France. [7] Department of Anaesthesiology and Surgical Intensive Care Medicine, CHU Beaujon, Clichy, Paris Diderot Sorbonne Cite University, France. [8] Intensive Care Unit, Centre Hospitalier Lyon Sud, Hospices Civils de Lyon, Pierre Bénite, France. [9] Service d'Anesthésie Réanimation, CHU Brabois, Nancy, France. [10] Pôle Anesthésie-Réanimation, CHU Reims, Reims, France. [11] Surgical Intensive Care Unit, CHU Cochin, Paris Descartes University, Paris, France. [12] Réanimation Polyvalente, CH Victor Dupouy, Argenteuil, France. [13] Service d'Anesthésie Réanimation Chirurgicale, CHU Besancon, Besançon, France. [14] Service d'Anesthésie et Réanimation Chirurgicale, Hotel Dieu, CHU Nantes, Nantes, France. [15] Service d'Anesthésie Réanimation, Hopital St Eloi, CHU Montpellier, Montpellier, France. [16] Département d'Anesthésie Réanimation, CHU Angers, L'UBL, Université d'Angers, Angers, France. [17] Critical Care Medicine Department, Amiens University Hospital, INSERM U1088, University of Picardy Jules Verne, Amiens, France. [18] Département d'Anesthésie-Réanimation, CHU Bichat Claude Bernard, 48 rue Henri Huchard, 75018 Paris, France.

Compliance with ethical standards

Conflicts of interest
Dr. Montravers reports personal fees and non-financial support from Astellas, AstraZeneca, Basilea, Bayer, Cubist, Menarini, MSD, Parexel, Pfizer, Tetraphase and The Medicines Company unrelated to the submitted work. Dr. Lescot reports grants, personal fees and non-financial support from Baxter, personal fees and non-financial support from Fresenius and personal fees from MSD unrelated to the submitted work. Dr. Paugam reports personal fees from MSD, Astellas and Baxter-Gambro unrelated to the submitted work. Dr. Lepape reports personal fees from Biomerieux unrelated to the submitted work. Dr. Blasco reports personal fees and non-financial support from Baxter, Astellas, Pfizer, MSD and Gilead unrelated to the submitted work. Dr. Asehnoune reports personal fees from LFB, Fresenius and Baxter unrelated to the submitted work. Dr. Jaber reports personal fees from Drager, Hamilton, Maquet and Fisher-Paykel unrelated to the submitted work. Dr. Lasocki reports research grants from Vifor Pharma and grants from LFB and Astellas unrelated to the submitted work. Dr. Dupont reports personal fees from Astellas, Pfizer, Gilead,

References

1. Barlam TF, Cosgrove SE, Abbo LM, MacDougall C, Schuetz AN, Septimus EJ, Srinivasan A, Dellit TH, Falck-Ytter YT, Fishman NO, Hamilton CW, Jenkins TC, Lipsett PA, Malani PN, May LS, Moran GJ, Neuhauser MM, Newland JG, Ohl CA, Samore MH, Seo SK, Trivedi KK (2016) Implementing an Antibiotic Stewardship Program: guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. Clin Infect Dis 62(e51–77):27080992
2. Sawyer RG, Claridge JA, Nathens AB, Rotstein OD, Duane TM, Evans HL, Cook CH, O'Neill PJ, Mazuski JE, Askari R, Wilson MA, Napolitano LM, Namias N, Miller PR, Dellinger EP, Watson CM, Coimbra R, Dent DL, Lowry SF, Cocanour CS, West MA, Banton KL, Cheadle WG, Lipsett PA, Guidry CA, Popovsky K (2015) Trial of short-course antimicrobial therapy for intraabdominal infection. N Engl J Med 372(1996–2005):25992746
3. Chow AW, Evans GA, Nathens AB, Ball CG, Hansen G, Harding GK, Kirkpatrick AW, Weiss K, Zhanel GG (2010) Canadian practice guidelines for surgical intra-abdominal infections. Can J Infect Dis Med Microbiol 21(11–37):21358883
4. Solomkin JS, Mazuski JE, Bradley JS, Rodvold KA, Goldstein EJ, Baron EJ, O'Neill PJ, Chow AW, Dellinger EP, Eachempati SR, Gorbach S, Hilfiker M, May AK, Nathens AB, Sawyer RG, Bartlett JG (2010) Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. Clin Infect Dis 50(133–164):20034345
5. Montravers P, Dupont H, Leone M, Constantin JM, Mertes PM, Laterre PF, Misset B, Bru JP, Gauzit R, Sotto A, Brigand C, Hamy A, Tuech JJ (2015) Guidelines for management of intra-abdominal infections. Anaesth Crit Care Pain Med 34(117–130):25922057
6. Eckmann C (2016) Antimicrobial therapy of intra-abdominal infections in the era of multiresistance. Chirurg 87:26–33
7. Sartelli M, Catena F, Abu-Zidan FM, Ansaloni L, Biffl WL, Boermeester MA, Ceresoli M, Chiara O, Coccolini F, De Waele JJ, Di Saverio S, Eckmann C, Fraga GP, Giannella M, Girardis M, Griffiths EA, Kashuk J, Kirkpatrick AW, Khokha V, Kluger Y, Labricciosa FM, Leppaniemi A, Maier RV, May AK, Malangoni M, Martin-Loeches I, Mazuski J, Montravers P, Peitzman A, Pereira BM, Reis T, Sakakushev B, Sganga G, Soreide K, Sugrue M, Ulrych J, Vincent JL, Viale P, Moore EE (2017) Management of intra-abdominal infections: recommendations by the WSES 2016 consensus conference. World J Emerg Surg 12(22):28484510
8. Mazuski JE, Tessier JM, May AK, Sawyer RG, Nadler EP, Rosengart MR, Chang PK, O'Neill PJ, Mollen KP, Huston JM, Diaz JJ Jr, Prince JM (2017) The Surgical Infection Society Revised Guidelines on the Management of Intra-Abdominal Infection. Surg Infect (Larchmt) 18(1–76):28085573
9. Dupont H, Friggeri A, Touzeau J, Airapetian N, Tinturier F, Lobjoie E, Lorne E, Hijazi M, Regimbeau JM, Mahjoub Y (2011) Enterococci increase the morbidity and mortality associated with severe intra-abdominal infections in elderly patients hospitalized in the intensive care unit. J Antimicrob Chemother 66(2379–2385):21791444
10. Seguin P, Laviolle B, Chanavaz C, Donnio PY, Gautier-Lerestif AL, Campion JP, Malledant Y (2006) Factors associated with multidrug-resistant bacteria in secondary peritonitis: impact on antibiotic therapy. Clin Microbiol Infect 12(980–985):16961634
11. Montravers P, Augustin P, Grall N, Desmard M, Allou N, Marmuse JP, Guglielminotti J (2016) Characteristics and outcomes of anti-infective de-escalation during health care-associated intra-abdominal infections. Crit Care 20(83):27052675
12. Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, Harbarth S, Hindler JF, Kahlmeter G, Olsson-Liljequist B, Paterson DL, Rice LB, Stelling J, Struelens MJ, Vatopoulos A, Weber JT, Monnet DL (2012) Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect 18(268–281):21793988
13. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonca A, Bruining H, Reinhart CK, Suter PM, Thijs LG (1996) The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med 22(707–710):8844239
14. Le Gall JR, Lemeshow S, Saulnier F (1993) A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. JAMA 270(2957–2963):8254858
15. Evans SR, Rubin D, Follmann D, Pennello G, Huskins WC, Powers JH, Schoenfeld D, Chuang-Stein C, Cosgrove SE, Fowler VG Jr, Lautenbach E, Chambers HF (2015) Desirability of Outcome Ranking (DOOR) and Response Adjusted for Duration of Antibiotic Risk (RADAR). Clin Infect Dis 61(800–806):26113652
16. Bouadma L, Luyt CE, Tubach F, Cracco C, Alvarez A, Schwebel C, Schortgen F, Lasocki S, Veber B, Dehoux M, Bernard M, Pasquet B, Regnier B, Brun-Buisson C, Chastre J, Wolff M (2010) Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. Lancet 375(463–474):20097417
17. van Buuren S, Groothuis-Oudshoorn K (2011) Mice: multivariate imputation by chained equations in R. J Stat Softw 45:1–67
18. De Waele JJ, Tellado JM, Weiss G, Alder J, Kruesmann F, Arvis P, Hussain T, Solomkin JS (2014) Efficacy and safety of moxifloxacin in hospitalized patients with secondary peritonitis: pooled analysis of four randomized phase III trials. Surg Infect (Larchmt) 15(567–575):24833256
19. Lucasti C, Popescu I, Ramesh MK, Lipka J, Sable C (2013) Comparative study of the efficacy and safety of ceftazidime/avibactam plus metronidazole versus meropenem in the treatment of complicated intra-abdominal infections in hospitalized adults: results of a randomized, double-blind. Phase II trial. J Antimicrob Chemother 68(1183–1192):23391714
20. Solomkin J, Hershberger E, Miller B, Popejoy M, Friedland I, Steenbergen J, Yoon M, Collins S, Yuan G, Barie PS, Eckmann C (2015) Ceftolozane/tazobactam plus metronidazole for complicated intra-abdominal infections in an era of multidrug resistance: results from a randomized, double-blind, phase 3 trial (ASPECT-cIAI). Clin Infect Dis 60(1462–1471):25670823
21. Solomkin JS, Ramesh MK, Cesnauskas G, Novikovs N, Stefanova P, Sutcliffe JA, Walpole SM, Horn PT (2014) Phase 2 randomized, double-blind study of the efficacy and safety of two dose regimens of eravacycline versus ertapenem for adult community-acquired complicated intra-abdominal infections. Antimicrob Agents Chemother 58(1847–1854):24342651
22. van Rossem CC, Schreinemacher MH, van Geloven AA, Bemelman WA (2016) Antibiotic duration after laparoscopic appendectomy for acute complicated appendicitis. JAMA Surg 151(323–329):26580850
23. De Waele J, Lipman J, Sakr Y, Marshall JC, Vanhems P, Barrera Groba C, Leone M, Vincent JL (2014) Abdominal infections in the intensive care unit: characteristics, treatment and determinants of outcome. BMC Infect Dis 14(420):25074742
24. Montravers P, Dufour G, Guglielminotti J, Desmard M, Muller C, Houissa H, Allou N, Marmuse JP, Augustin P (2015) Dynamic changes of microbial flora and therapeutic consequences in persistent peritonitis. Crit Care 19(70):25887649
25. Sartelli M, Catena F, Ansaloni L, Coccolini F, Corbella D, Moore EE, Malangoni M, Velmahos G, Coimbra R, Koike K, Leppaniemi A, Biffl W, Balogh Z, Bendinelli C, Gupta S, Kluger Y, Agresta F, Di Saverio S, Tugnoli G, Jovine E, Ordonez CA, Whelan JF, Fraga GP, Gomes CA, Pereira GA, Yuan KC, Bala M, Peev MP, Ben-Ishay O, Cui Y, Marwah S, Zachariah S, Wani I, Rangarajan M, Sakakushev B, Kong V, Ahmed A, Abbas A, Gonsaga RA, Guercioni G, Vettoretto N, Poiasina E, Diaz-Nieto R, Massalou D, Skrovina M, Gerych I, Augustin G, Kenig J, Khokha V, Trana C, Kok KY, Mefire AC, Lee JG, Hong SK, Lohse HA, Ghnnam W, Verni A, Lohsiriwat V, Siribumrungwong B, El Zalabany T, Tavares A, Baiocchi G, Das K, Jarry J, Zida M, Sato N, Murata K, Shoko T, Irahara T, Hamedelneel AO, Naidoo N, Adesunkanmi AR, Kobe Y, Ishii W, Oka K, Izawa Y, Hamid H, Khan I, Attri A, Sharma R, Sanjuan J, Badiel M, Barnabe R (2014) Complicated intra-abdominal infections

worldwide: the definitive data of the CIAOW Study. World J Emerg Surg 9(37):24883079

26. Seguin P, Fedun Y, Laviolle B, Nesseler N, Donnio PY, Malledant Y (2010) Risk factors for multidrug-resistant bacteria in patients with post-operative peritonitis requiring intensive care. J Antimicrob Chemother 65(342–346):20008043

27. Riche FC, Dray X, Laisne MJ, Mateo J, Raskine L, Sanson-Le Pors MJ, Payen D, Valleur P, Cholley BP (2009) Factors associated with septic shock and mortality in generalized peritonitis: comparison between community-acquired and postoperative peritonitis. Crit Care 13(R99):19552799

28. Jung B, Molinari N, Nasri M, Hajjej Z, Chanques G, Jean-Pierre H, Panaro F, Jaber S (2013) Procalcitonin biomarker kinetics fails to predict treatment response in perioperative abdominal infection with septic shock. Crit Care 17(R255):24156734

29. Goldmann DA, Weinstein RA, Wenzel RP, Tablan OC, Duma RJ, Gaynes RP, Schlosser J, Martone WJ (1996) Strategies to prevent and control the emergence and spread of antimicrobial-resistant microorganisms in hospitals. A challenge to hospital leadership. JAMA 275(234–240):8604178

30. Augustin P, Tran-Dinh A, Valin N, Desmard M, Crevecoeur MA, Muller-Serieys C, Woerther PL, Marmuse JP, Bronchard R, Montravers P (2013) *Pseudomonas aeruginosa* post-operative peritonitis: clinical features, risk factors, and prognosis. Surg Infect (Larchmt) 14(297–303):23672242

31. Chastre J, Wolff M, Fagon JY, Chevret S, Thomas F, Wermert D, Clementi E, Gonzalez J, Jusserand D, Asfar P, Perrin D, Fieux F, Aubas S (2003) Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial. JAMA 290(2588–2598):14625336