BJA

British Journal of Anaesthesia, 117 (1): 66–72 (2016)

doi: 10.1093/bja/aew117
Clinical Practice

Compliance with an empirical antimicrobial protocol improves the outcome of complicated intra-abdominal infections: a prospective observational study

M. Guilbart[1,†], E. Zogheib[1,3,†], A. Ntouba[1], L. Rebibo[2], J. M. Régimbeau[2], Y. Mahjoub[1,3] and H. Dupont[1,3,*]

[1]Department of Anaesthesiology and Critical Medicine, [2]Department of Digestive and Metabolic Surgery, Amiens University Hospital, Amiens, France, and [3]INSERM UMR 1088, Jules Verne University Picardy, Amiens, France

*Corresponding author. E-mail: dupont.herve@chu-amiens.fr

Abstract

Background: Despite improvements in medical and surgical care, mortality attributed to complicated intra-abdominal infections (cIAI) remains high. Appropriate initial antimicrobial therapy (ABT) is key to successful management. The main causes of non-compliance with empirical protocols have not been clearly described.

Methods: An empirical ABT protocol was designed according to guidelines, validated in the institution and widely disseminated. All patients with cIAI (2009–2011) were then prospectively studied to evaluate compliance with this protocol and its impact on outcome. Patients were classified into two groups according to whether or not they received ABT in compliance with the protocol.

Results: 310 patients were included: 223 (71.9%) with community-acquired and 87 (28.1%) with healthcare-associated cIAI [mean age 60(17–97) yr, mean SAPS II score 24(16)]. Empirical ABT complied with the protocol in 52.3% of patients. The appropriateness of empirical ABT to target the bacteria isolated was 80%. Independent factors associated with non-compliance with the protocol were the anaesthetist's age ≥36 yr [OR 2.1; 95%CI (1.3–3.4)] and the presence of risk factors for multidrug-resistant bacteria (MDRB) [OR 5.4; 95%CI (3.0–9.5)]. Non-compliance with the protocol was associated with higher mortality (14.9 *vs* 5.6%, *P*=0.011) and morbidity: relaparotomy (*P*=0.047), haemodynamic failure (*P*=0.001), postoperative pneumonia (*P*=0.025), longer duration of mechanical ventilation (*P*<0.001), longer ICU stay (*P*<0.001) and longer hospital stay (*P*=0.002). On multivariate logistic regression analysis, non-compliance with the ABT protocol was independently associated with mortality [OR 2.4; 95% CI (1.1–5.7), *P*=0.04].

Conclusions: Non-compliance with empirical ABT guidelines in cIAI is associated with increased morbidity and mortality. Information campaigns should target older anaesthetists and risk factors for MDRB.

Key words: antimicrobial agent; outcome; protocol compliance; secondary peritonitis

[†]These authors contributed equally to the study.

Accepted: March 5, 2016

Editor's key points

- This study evaluated the whether compliance with an antimicrobial protocol affected outcome in patients with intra-abdominal infections.
- Non-compliance with the protocol was associated with worse clinical outcomes in a single centre.
- Anaesthetist's age and several clinical factors were associated with non-compliance.
- More work is needed to determine how compliance can be improved.

Despite improvements in surgical and medical care, particularly progress in antibiotic therapy, the mortality attributed to secondary peritonitis remains high, between 4 and 30%, depending on the severity and the site of infection.[1–4] These infections represent the second leading septic cause of ICU admission after respiratory tract infections,[5] and the third leading cause of septic shock.[6] Secondary peritonitis comprises a broad range of pathological conditions, including community-acquired peritonitis and nosocomial peritonitis (including postoperative peritonitis). The keys to successful management are early diagnosis, appropriate surgical intervention, and administration of systemic antibiotics that are effective against both aerobic and anaerobic bacteria.[7] Surgical treatment usually consists of laparotomy to eliminate the source of infection, intraoperative peritoneal lavage to reduce the bacterial load, and drainage for prevention of persistent or recurrent infection.[8] Seiler and colleagues[9]. reported an increase of mortality rates from 13 to 27% depending on the adequacy of surgery, with reoperation rates ranging from 9 to 32%. Early empirical antibiotic therapy is a well-established recommendation.[7] Kumar and colleagues[6] reported that the survival rate decreased by 7.6% per h when antibiotic therapy was delayed in patients with septic shock. Most studies of intra-abdominal infections have shown that appropriate empirical antibiotic therapy improved the clinical success rate and reduced the length of hospital stay and overall costs.[10 11] However, when empirical antibiotic therapy is inappropriate, patients may require reoperation, resulting in a poorer outcome[12–17] and an increased likelihood of multidrug-resistant bacteria (MDRB) such as *Pseudomonas aeruginosa* and yeasts.[14 18]

Education and stewardship of rational antibiotic use in France, have become a major public health challenge for the World Health Organization (WHO) and the European Community over recent yr. Most published studies have evaluated clinical practice in relation to implementation of antibiotic prescription protocols, and have demonstrated an improvement antibiotic prescription practices.[19] After a local evaluation of prescription practices in community-acquired peritonitis demonstrated a high rate of inappropriate empirical antimicrobial therapy, an antibiotic protocol was established for use in emergency operating rooms with a planned follow-up assessment. The aim of the present study was to assess the main causes of non-compliance with the antimicrobial protocol for complicated intra-abdominal infections (cIAI) and to assess its relationship with outcome.

Methods

Study design and patients

A single-centre, prospective study was conducted in all patients with complicated intra-abdominal infections (cIAI) treated at our institution between January 2009 and December 2011. This study was approved by the local ethics committee. According to French law, informed consent was waived because of the observational, non-interventional nature of the study.

Patients under the age of 18 yr, with primary peritonitis (medical causes of intra-abdominal infection not requiring surgical therapy such as infected ascites), infected acute pancreatitis, postoperative nosocomial infection, and acute traumatic perforation <6 h were not included in the study.

All patients in the period were consecutively included according to the registry of the emergency operating room.

Surgery and microbiological management

Surgery was performed by an experienced team according to the same guidelines for the management of cIAI. Laparoscopy or laparotomy was performed depending on the diagnosis and as decided by the surgeon responsible. All peritoneal fluid samples were systematically sent to the microbiology and mycology departments. Antimicrobial therapy was initiated as soon as possible according to our empirical protocol. At least one set of blood cultures were obtained preoperatively. Culture and antibiotic susceptibility testing were performed in the microbiology department.

Definitions and protocol

The empirical antimicrobial therapy protocol (Table 1) was established in agreement with the hospital's infection control committee and was then displayed in operating rooms. All surgeons and anaesthetists involved in the emergency operating room (OR) were informed about this protocol by e-mail and at meetings and the protocol was posted in the OR.

A complicated intra-abdominal infection was defined as a complicated intra-abdominal infection extending beyond the hollow viscus of origin into the peritoneal space and associated

Table 1 Empirical antimicrobial protocol in community-acquired and healthcare-associated complicated intra-abdominal infections. MDRB, multidrug resistant bacteria

Risk factor for MDRB	Beta-lactam allergy	Illness severity	
		No	Yes
No	No	Cefotaxime or Ceftriaxone+metronidazole OR Amoxicillin/clavulanate+gentamicin	Piperacillin/tazobactam+gentamicin
	Yes	Levofloxacin+metronidazole	Levofloxacin+metronidazole+gentamicin
Yes	No	Ertapenem	Imipenem+vancomycin+amikacin
	Yes	Tigecycline	Tigecycline+ciprofloxacin

either with abscess formation or with peritonitis, according to established guidelines.[8]

Risk factors for multidrug-resistant bacteria (MDRB) were defined as previous use of antibiotics (≤3 months), previous hospitalization (≤6 months), current hospitalization for more than 48 h, or institutionalized patients. Such patients were considered to constitute healthcare-associated cIAI.

Illness severity was defined as the presence of haemodynamic failure (hypotension despite fluid resuscitation, need for norepinephrine), immunosuppression, malnutrition (BMI≤18.5 kg m^{-2}) or surgery delayed for more than 12 h.

Data collection

The following data were collected: patient characteristics (age, gender, BMI, ASA score[20]), underlying disease (cardiovascular disease, malignancy or immunosuppression, chronic renal failure, diabetes mellitus, abdominal surgery), allergy to beta-lactams. On the day of surgery, the severity of infection was assessed by the Acute Physiology and Chronic Health Evaluation II score,[21] Simplified Acute Physiology Score II score,[22] Organ System Failure score[23] and Mannheim Peritonitis Index.[24] The type (community-acquired or healthcare-associated), aetiology, and primary site of infection (upper or lower gastrointestinal tract) responsible for cIAI were recorded. The mesocolon was considered to be the barrier between the upper and lower gastrointestinal tract. Peritoneal fluid was placed in sterile, dry, BacT / ALERT® anaerobic blood culture bottles (BioMerieux laboratories, Durham, USA) and BACTEC™ Mycosis-IC/F (Becton, Dickinson and Company, Sparks, USA), and sent to the microbiology and mycology laboratory. Main complications, duration of mechanical ventilation, need for relaparotomy, death and length of stay were also reported.

Outcome

Compliance with the protocol was recorded. Non-compliance was defined as failure to comply with illness severity, MDRB risk factors or β-lactam allergy. Appropriateness of empirical antimicrobial therapy except for yeasts was determined by antimicrobial susceptibility testing. Treatment of *Candida* was left to the attending physician's discretion according to a specific hospital protocol. Compliance with anti-fungal treatment was not assessed.

For the study, cardiovascular failure was defined by the need for vasopressor during surgery (norepinephrine) despite fluid challenge. Respiratory failure was defined by the need for more than one day of mechanical ventilation. ICU admission, lengths of stay (ICU, hospital) and hospital mortality were assessed.

Statistical analysis

Results are expressed as mean (SD) or number (percentage). In the first part of the study, patients were compared according to compliance or non-compliance with the empirical antibiotic therapy protocol. Univariate analysis was performed using Mann-Whitney *U*-test and χ^2 tests with Yates' correction. Two multivariate stepwise logistic regression models (Backward Wald model) were built, in order first to identify any independent factors of inappropriate empirical therapy and second to identify independent factors of mortality.[25] Only significant variables (P<0.05) in the univariate analysis were included in the multivariate model. All potential explanatory variables, included in the multivariate analyses, were subjected to a collinearity analysis in a correlation matrix. Intercorrelated variables were not included in the multivariate model (tolerance <0.3 and variance inflation factor >3). Adjusted odds ratios (ORs) and their 95% confidence intervals (95%CIs) are reported. The constant (intercept) was only included in the model when statistically significant. The Hosmer-Lemeshow test was used to assess the model's goodness of fit. The statistical significances of individual regression coefficients were assessed with the Wald χ^2test. The model's predicted probabilities were validated with the c statistic (corresponding to the model's area under the curve). Statistical analysis was performed with PASW Statistics 18 software (IBM, Chicago, USA) and MedCalc 12.7.5 (MedCalc Software, Ostend, Belgium).

Results

During the study period, 310 patients with complicated intra-abdominal infections were included: 223 (71.9%) with community-acquired (CA) and 87 (28.1%) with healthcare-associated (HA) cIAI. The mean age of the population was 60(22) yr and mean SAPS II score was 24(16) with an observed mortality of 10%. The sites and main causes of cIAI were upper gastrointestinal tract for 96 (31%), mainly biliary tract (58, 18.7%) and ulcer disease (30, 9.7%); and lower intestinal tract for 214 (69%), mainly appendicitis (99, 31.9%) and diverticulitis (55, 17.7%). cIAI were localized in 57.7% of patients (179/310) with a mean MPI of 15.2 (8.5). Peritoneal fluid samples were obtained in 93.5% of patients (290/310). The rate of positive microbiological culture was 74.5% (216/290). Microbiological characteristics of peritoneal fluid are presented in Table 2. Five hundred and seventy-four pathogens were identified, mainly *Escherichia coli* (32.2%), *Enterococci* spp (14%), *Streptococci* spp (12.2%), and *Bacteroides* spp (11.9%). Yeasts were found in 6.9% of isolates (72.5% of *Candida albicans*).

Compliance with the protocol

Of the 310 patients included, 308 (99.4%) received empirical antimicrobial therapy during surgery. Antibiotic prescription complied with the protocol in 52.3% of patients [95%CI (46.7–57.8%)] and was effective against the microorganisms isolated in 80% of patients [95%CI (75.4–84.6%)]. No major difference was observed between the group of patients who received appropriate ABT according to microbiological culture and the group of inappropriate ABT, except more infectious complications in the former group (24.6% *vs* 43.1%, P=0.008). Patients with risks factors of MDRB had more resistant infections (39/184 isolates, 21.1%) than those without risk factors (45/350, 12.8%), P=0.02. When considering patients, and not isolates, the rate of MDRB was 35.7% in the group with risk factors *vs* 18.9% in the group without risk factors (P=0.003).The resistance rate to first line ABT according to the protocol was 18.9% in the low risk group and 15.5% in the high-risk group. Non-compliance with the protocol was associated with an increased rate of inappropriate antimicrobial therapy (27.7% *vs* 12.7%, P=0.002). The majority of cases of non-compliance with the protocol concerned an insufficient spectrum (75.7%): 32/37 (86.5%) for the MRDB risk factors, 56/81 (69.1%) for illness severity, 2/2 (100%) for ß-lactam allergy, 20/26 (76.9%) for both MDRD risk factors and illness severity, and 2/2 for the lack of ABT prescription.

Predictive factors for non-compliance with the protocol

Patients who received inappropriate antimicrobial therapy according to the protocol were older [63(21) *vs* 57(22) yr, P=0.04],

Table 2 Microbiological characteristics of peritoneal fluid and number of resistant isolates according to first line antimicrobial therapy of the protocol in groups with and without risk factors of multidrug resistant bacteria. Data are expressed as number (proportion, in %) of isolates. MDRB, multidrug resistant bacteria

	Isolates (*n*=574)	Risk factors for MDRB (*n*=205)	No risk factors for MDRB (*n*=369)
Aerobes	**447** (77.9)	13	47
Gram-negative bacilli	**288** (50.2)	0	41
E. coli	185 (32.2)	0	12
Klebsiella spp	29 (5)	0	0
Enterobacter spp	9 (1.5)	0	6
Proteus spp	17 (2.9)	0	1
Morganella morganii	12 (2.1)	0	6
Hafnia alvei	7 (1.2)	0	4
Citrobacter spp	11 (1.9)	0	3
Pseudomonas aeruginosa	16 (2.8)	0	9
Miscellaneous	4 (0.6)	0	0
Gram-positive cocci	**159** (27.7)	13	6
Streptococci	70 (12.2)	0	1
Staphylococci	9 (1.5)	0	4
Enterococci	80 (14)	13	1
Anaerobes	**87** (15.2)	0	1
Bacteroides	68 (11.9)	0	1
Clostridium	7 (1.2)	0	0
Miscellaneous	12 (2.1)	0	0
Fungi	**40** (6.9)	NA	NA
Candida albicans	29 (5)		
Candida glabrata	5 (0.9)		
Candida tropicalis	4 (0.6)		
Candida krusei	1 (0.2)		
Miscellaneous	1 (0.2)		

Table 3 Main characteristics of the population according to compliance with the protocol. Values are expressed as mean (SD) or number (proportion, in %) or median [25–75]. APACHE II, Acute Physiology And Chronic Health Evaluation II; MDRB, multidrug-resistant bacteria; SAPS 2, Simplified Acute Physiology Score II; SOFA, Sepsis-related Organ Failure Assessment

	Compliance (*n*=162)	Non-compliance (*n*=148)	P Value
Age, yr	57 (17–97)	63 (17–96)	0.04
Female	72 (44.4)	80 (54.1)	0.115
BMI, kg.m^{-22}	26 (5.3)	26 (6.7)	0.638
ASA status	2 [1-4]	3 [1-5]	0.005
Underlying disease			
Abdominal surgery	25 (15.4)	31 (20.9)	0.266
Diabetes mellitus	25 (15.4)	22 (14.9)	0.984
Malignancy and immunosuppression	11 (6.8)	10 (6.8)	0.830
Cardiovascular disease	68 (42)	83 (56.1)	0.018
Chronic renal failure	4 (2.5)	9 (6.1)	0.193
Smoker	53 (32.7)	51 (34.5)	0.838
Beta-lactam allergy	10 (6.2)	6 (4.1)	0.558
Risk factor for MDRB	22 (13.6)	65 (43.9)	<0.001
Illness severity	36 (22.2)	51 (34.5)	0.023
Preoperative cardiovascular failure	15 (9.3)	25 (16.9)	0.067
Temperature	37.6 (0.8)	37.9 (0.8)	0.054
Mannheim Peritonitis Index score	15.4 (8.4)	18 (8.4)	0.008
Localized peritonitis	96 (59.3)	83 (56.1)	0.652
Upper gastrointestinal tract origin	45 (27.8)	51 (34.5)	0.251
Ongoing antimicrobial therapy ≥48 h	17 (10.5)	33 (22.3)	0.008
SAPS II score	23 (15)	29 (17)	<0.001
APACHE II score	7.1 (7.7)	10.6 (9.3)	<0.001
SOFA score	1.4 (3.1)	2.5 (3.9)	<0.001

with more cardiovascular morbidity (56% *vs* 42%, *P*=0.018), and presented more severe illness (34.5% *vs* 22.2%, *P*=0.023) or risk factors for MDRB (43.9% *vs* 13.6%, *P*<0.001). Anaesthetists, who were the main prescribers, were also older [40(7) *vs* 37(6) yr, *P*<0.001] in the case of non-compliance with the protocol (Table 3). The main laboratory results were not statistically different according to

Table 4 Independent risk factors for non-compliance with the protocol. OR, odds ratio; CI, confidence interval; aOR, adjusted odds ratio; ABT, antimicrobial therapy; APACHE II, Acute Physiology And Chronic Health Evaluation II; MDRB, multidrug-resistant bacteria; SAPS 2, Simplified Acute Physiology Score II; SOFA, Sepsis-related Organ Failure Assessment

Parameters	OR [95%CI]	aOR [95%CI]	P value
Anaesthetist's age ≥36, yr	1.84 [1.17–2.90]	2.11 [1.29–3.43]	0.003
Patient's age ≥62, yr	1.78 [1.13–2.79]	–	
Illness Severity criteria	1.84 [1.11–3.04]	–	
Risk factor for MDRB	4.98 [2.86–8.88]	5.38 [3.05–9.50]	<0.001
Cardiovascular history	1.76 [1.12–2.77]	–	
ASA score ≥3	2.06 [1.31–3.25]	–	
Mannheim Peritonitis Index >16	1.51 [0.96–2.37]	–	
SOFA score ≥3	2.36 [1.34–4.12]	–	
SAPS II score >23	1.97 [1.25–3.09]	–	
APACHE II score >6	2.01 [1.28–3.16]	–	
Ongoing ABT ≥48 h	2.45 [1.30–4.61]	–	

Table 5 Main outcomes after surgery according to compliance with the protocol. Values are expressed as mean (SD) or proportions. ICU, intensive care unit; MV, mechanical ventilation; LOS, length of stay

	Compliance (*n*=162)	Non-compliance (*n*=148)	P Value
Complications	45 (27.8)	90 (60.8)	<0.001
Non-infectious complications	27 (16.7)	63 (42.6)	<0.001
Infectious complications	32 (19.8)	56 (37.8)	<0.001
Wound abscess	12 (7.4)	15 (10.1)	0.516
Pneumonia	12 (7.4)	24 (16.2)	0.025
Transfusion	9 (5.6)	21 (14.2)	0.018
Relaparotomy	15 (9.3)	26 (17.6)	0.047
ICU admission	37 (22.8)	61 (41.2)	<0.001
Cardiovascular failure	19 (11.7)	40 (27)	0.001
Respiratory failure	17 (10.5)	37 (25)	0.001
Duration of MV, days	1.6 (6.5)	4.2 (11.6)	<0.001
ICU LOS, days	1.8 (5.2)	6.2 (13.9)	<0.001
Hospital LOS, days	11.5 (11.7)	18.7 (23.4)	0.002
Mortality	9 (5.6)	22 (14.9)	0.011

compliance or non-compliance with the protocol (data not shown). Reasons for non-compliance were not strictly the same between the group with risk factors of MRDB (illness severity, higher temperature and anaesthetist's age) and the group without risk factors (history of chronic renal failure, illness severity, preoperative cardiovascular failure and anaesthetist's age). There was no relationship between the anesthetist's age and illness severity (*P*=0.21) nor with high risk of MDRB (*P*=0.61). Multivariate analysis identified two independent risk factors for non-compliance with the protocol: presence of risk factors for MDRB (*P*<0.001), and anaesthetist's age with a mean cut-off of 36 yr (*P*=0.003) (Table 4).

Impact of non-compliance with the protocol

Non-compliance with the protocol was associated with poorer outcomes (Table 5): subsequent surgery (17.6% *vs* 9.3%, *P*=0.047), higher rate of postoperative haemodynamic failure (27.0% *vs* 11.7%, *P*=0.001), higher rate of postoperative pneumonia (16.2% *vs* 7.4%, *P*=0.025), increased duration of mechanical ventilation [4(12) d *vs* 2(6), *P*<0.001], increased length of stay in ICU [6(14) d *vs* 2(5), *P*<0.001] and in hospital [19(23) d *vs* 11(12), *P*=0.002]. Overall mortality was also higher (14.9% *vs* 5.6%, *P*=0.011). In multivariate analysis, three factors remained independently associated with mortality: non-compliance with the protocol [OR=2.4, 95%CI=(1.1–5.7), *P*=0.04], APACH II score >7 [OR=12.3, 95%CI=(3.6–41.8), *P*=0.0001] and generalized peritonitis [OR=3.4, 95%CI=(1.4–8.1), *P*=0.005]. The wald χ^2 of the model was 45.12 (ddl=3, *P*=0.0001). The Hosmer Lemeshow test was 2.12 (ddl=6, *P*=0.91) and the *c* statistic of the model was 0.835 [95% CI=(0.775—0.896)].

Discussion

This study demonstrated an improvement of medical practices after implementation of an empirical antimicrobial therapy protocol, in community-acquired and hospital-associated cIAI, but the protocol non-compliance rate remained high (47.7%) and was associated with increased morbidity and mortality. Two variables were independently associated with non-compliance with this protocol: presence of risk factors for MDRB and anaesthetist's age more than 36 yr.

Several studies have reported the benefit of implementing an antibiotic protocol reflecting the real interest in stewardship of antibiotic use.[19 26] Raymond and colleagues[19] in 2011 reported inadequacy of antibiotic prescriptions with respect to national guidelines in 74% of patients. After establishing a process explaining how to initiate and manage antibiotic therapy, this rate fell to 43% after 2 yr. In our study, recommendations concerning antibiotic prescriptions were more strictly observed after implementation of the protocol. Nevertheless, 47.7% of prescriptions were still inappropriate, which is an excessively high rate in view of the consequences. One reason may be related to the study procedures. Patients were operated in the emergency operating room, which operates continuously 24 h a day, 7 days a week, with an on-site day care system. This organization involves a large number of physicians and potential prescribers, some of whom may not have been informed about this protocol. The rate of non-compliance we observed is higher than that reported in a multicentre study, evaluating guidelines for treating MDR pneumonia, which was 42.6%.[27] However, mortality was higher in the compliant group when compared with the non-compliant, raising questions over the accuracy of the protocol.

In this study, most cases of non-compliance with the protocol were related to an insufficient spectrum. Amoxicillin/clavulanate without the addition of an aminoglycoside was the most common observed non-compliance (28/148 or 18.9% of patients). We hypothesized that physicians did not use an aminoglycoside because of a poor understanding of the local microbial ecology, or fear of inducing acute kidney injury in patients with relative hypovolaemia. *Escherichia coli* strains presented a high rate of resistance to Amoxicillin (45.9%) and Amoxicillin/clavulanate (11.3%), as described in the literature.[28] It was therefore legitimate to recommend the addition of gentamicin to restore sensitivity and bactericidal effect. In contrast, 24.3% of inappropriate antibiotic prescriptions corresponded to an excessively broad spectrum. These prescriptions were likely related to the perceived severity of the illness.[29] Moreover, in the emergency setting, physicians may not have access to all information concerning the patient's history, particularly the length of hospital stay, other infections or ongoing antimicrobial therapy. The presence of risk factors for MDRB may therefore predispose to inappropriate antibiotic prescription. Previous antibiotic therapy initiated for another infection was usually maintained, which is probably why a large number of atypical antibiotic combinations were observed.

Few studies have evaluated independent risk factors associated with non-compliance of a protocol. It is important to recognize the key factors determining prescribing behaviour and the incentives to change this behaviour and to incorporate these elements into stewardship programmes. The second independent risk factor associated with non-compliance with the protocol was the anaesthetist's age. The non-compliance rate increased with increasing age of the anaesthetists. Cadieux and colleagues[30] found that physicians with high-volume practices and those who had been in practice for a long time were more likely to prescribe antibiotics inappropriately. It has also been suggested that the physician training environment, possibly related to traditional professional practices, cultural expectations or pharmaceutical detailing, was responsible for prescribing differences. The present study comprised 36 different prescribers, each with their own experiences and education. Despite evidence-based recommendations, adherence to guidelines does not constitute the best therapeutic choice in each and every patient.[31] Subjects' clinical conditions and co-morbidities vary widely, sometimes making the 'recommended' drug a non-applicable strategy.

Antimicrobial stewardship programmes have markedly improved antimicrobial prescription practices and patient outcomes with the use of 'top-down' methods, such as formulary restriction and prospective audit with feedback.[32] We believe that these programmes should part of continuing medical education and we emphasize the importance of active involvement of all members of the health care unit, including nurses, pharmacists, and physicians.

Our study has a number of potential limitations. Firstly, this was a single-centre study. Our centre is a large tertiary referral centre with teams experienced in the management of complicated-intra abdominal infections and nearly all patients in our series received antibiotics, but our results must be validated by multicentre trials. As no interim analysis was performed, we therefore had little direct influence on compliance with the protocol. The observational nature of the study may be another bias, especially when considering mortality and a randomized trial would be required. However, use of a control group could raise possible ethical concerns. Some data may be missing, particularly concerning certain patient characteristics, which may explain why some patients were classified as not allergic to beta-lactams, but nevertheless received fluoroquinolones. The duration and modifications of antibiotic therapy were not evaluated, although they are known to influence outcomes because we wanted to focus exclusively on what happens in the emergency operating room.[16 30]

Conclusion

Establishment of an empirical antimicrobial protocol for complicated intra-abdominal infections in the emergency operating room improved clinical practices and compliance with national prescribing guidelines. Non-compliance with the protocol was associated with increased morbidity and mortality. Information must be targeted to anaesthetists 36 yr and older and in the presence of MDRB risk factors.

Authors' contributions

Study design/planning: H.D., M.G., E.Z.
Study conduct:M.G., A.N., L.R., J.M.R., E.Z., Y.M.
Data analysis:M.G., E.Z., H.D., Y.M.
Writing paper: M.G., E.Z., H.D., Y.M.
Revising paper: all authors

Declaration of interest

None declared.

References

1. Cavallaro A, Catania V, Cavallaro M, Zanghi A, Cappellani A. Management of secondary peritonitis: our experience. *Ann Ital Chir* 2008; **79**: 255–60
2. Dupont H, Carbon C, Carlet J. Monotherapy with a broad-spectrum beta-lactam is as effective as its combination with an aminoglycoside in treatment of severe generalized peritonitis: a multicenter randomized controlled trial. The Severe Generalized Peritonitis Study Group. *Antimicrob Agents Chemother* 2000; **44**: 2028–33
3. Gauzit R, Pean Y, Barth X, Mistretta F, Lalaude O, Top Study T. Epidemiology, management, and prognosis of secondary non-postoperative peritonitis: a French prospective observational multicenter study. *Surg Infect (Larchmt)* 2009; **10**: 119–27
4. Montravers P, Chalfine A, Gauzit R, *et al*. Clinical and therapeutic features of nonpostoperative nosocomial intra-abdominal infections. *Ann Surg* 2004; **239**: 409–16

5. Vincent JL, Sakr Y, Sprung CL, *et al*. Sepsis in European intensive care units: results of the SOAP study. *Crit Care Med* 2006; **34**: 344–53
6. Kumar A, Roberts D, Wood KE, *et al*. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med* 2006; **34**: 1589–96
7. Dellinger RP, Levy MM, Carlet JM, *et al*. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Intensive Care Med* 2008; **34**: 17–60
8. Solomkin JS, Mazuski JE, Bradley JS, *et al*. 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* 2010; **50**: 133–64
9. Seiler CA, Brugger L, Forssmann U, Baer HU, Buchler MW. Conservative surgical treatment of diffuse peritonitis. *Surgery* 2000; **127**: 178–84
10. Barie PS. The cost of failure. *Surg Infect (Larchmt)* 2008; **9**: 313–5
11. Davey PG, Marwick C. Appropriate vs. inappropriate antimicrobial therapy. *Clin Microbiol Infect* 2008; **14**(Suppl 3): 15–21
12. Edelsberg J, Berger A, Schell S, Mallick R, Kuznik A, Oster G. Economic consequences of failure of initial antibiotic therapy in hospitalized adults with complicated intra-abdominal infections. *Surg Infect (Larchmt)* 2008; **9**: 335–47
13. Fitousis K, Moore LJ, Hall J, Moore FA, Pass S. Evaluation of empiric antibiotic use in surgical sepsis. *Am J Surg* 2010; **200**: 776–82; discussion 82
14. Krobot K, Yin D, Zhang Q, *et al*. Effect of inappropriate initial empiric antibiotic therapy on outcome of patients with community-acquired intra-abdominal infections requiring surgery. *Eur J Clin Microbiol Infect Dis* 2004; **23**: 682–7
15. Kumar A, Ellis P, Arabi Y, *et al*. Initiation of inappropriate antimicrobial therapy results in a fivefold reduction of survival in human septic shock. *Chest* 2009; **136**: 1237–48
16. Micek ST, Welch EC, Khan J, *et al*. Empiric combination antibiotic therapy is associated with improved outcome against sepsis due to Gram-negative bacteria: a retrospective analysis. *Antimicrob Agents Chemother* 2010; **54**: 1742–8
17. Sturkenboom MC, Goettsch WG, Picelli G, *et al*. Inappropriate initial treatment of secondary intra-abdominal infections leads to increased risk of clinical failure and costs. *Br J Clin Pharmacol* 2005; **60**: 438–43
18. Seguin P, Laviolle B, Chanavaz C, *et al*. Factors associated with multidrug-resistant bacteria in secondary peritonitis: impact on antibiotic therapy. *Clin Microbiol Infect* 2006; **12**: 980–5
19. Raymond S, Bourdelin M, Becker M, *et al*. [Antibiotics in elderly patients: Impact of clinical practice evaluation]. *Med Mal Infect* 2011; **41**: 330–5
20. Owens WD, Felts JA, Spitznagel EL. ASA physical status classifications: a study of consistency of ratings. *Anesthesiology* 1978; **49**: 239–43
21. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med* 1985; **13**: 818–29
22. Le Gall JR, Lemeshow S, Saulnier F. A new simplified acute physiology score (SAPS II) based on a European-North American multicenter study. *JAMA* 1993; **270**: 29057–68
23. Vincent JL, Moreno R, Takala J, *et al*. 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* 1996; **22**: 707–10
24. Linder MM, Wacha H, Feldmann U, Wesch G, Streifensand RA, Gundlach E. The Mannheim peritonitis index. An instrument for the intraoperative prognosis of peritonitis. *Chirurg* 1987; **58**: 84–92
25. Peng C, Lee K, Ingersoll G. An introduction to logistic regression analysis and reporting. *J Educ Res* 2002; **96**: 1–14
26. Popovski Z, Mercuri M, Main C, *et al*. Multifaceted intervention to optimize antibiotic use for intra-abdominal infections. *J Antimicrob Chemother* 2015; **70**: 1226–9
27. Kett DH, Cano E, Quartin AA, *et al*. Implementation of guidelines for management of possible multidrug-resistant pneumonia in intensive care: an observational, multicentre cohort study. *Lancet Infect Dis* 2011; **11**: 181–9
28. Sotto A, Lefrant JY, Fabbro-Peray P, *et al*. Evaluation of antimicrobial therapy management of 120 consecutive patients with secondary peritonitis. *J Antimicrob Chemother* 2002; **50**: 569–76
29. van Buul LW, van der Steen JT, Doncker SM, *et al*. Factors influencing antibiotic prescribing in long-term care facilities: a qualitative in-depth study. *BMC Geriatr* 2014; **14**: 136
30. Cadieux G, Tamblyn R, Dauphinee D, Libman M. Predictors of inappropriate antibiotic prescribing among primary care physicians. *CMAJ* 2007; **177**: 877–83
31. Pagano L, Caira M, Offidani M, *et al*. Adherence to international guidelines for the treatment of invasive aspergillosis in acute myeloid leukaemia: feasibility and utility (SEIFEM-2008B study). *J Antimicrob Chemother* 2010; **65**: 2013–8
32. Hamilton KW, Gerber JS, Moehring R, *et al*. Point-of-prescription interventions to improve antimicrobial stewardship. *Clin Infect Dis* 2015; **60**: 1252–8

Handling editor: J. P. Thompson