Aggressive versus conservative initiation of antimicrobial treatment in critically ill surgical patients with suspected intensive-care-unit-acquired infection: a quasi-experimental, before and after observational cohort study

Tjasa Hranjec, Laura H Rosenberger, Brian Swenson, Rosemarie Metzger, Tanya R Flohr, Amani D Politano, Lin M Riccio, Kimberley A Popovsky, Robert G Sawyer

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Department of Surgery, University of Virginia, Charlottesville, VA, USA (T Hranjec MD, L H Rosenberger MD, B Swenson MD, R Metzger MD, T R Flohr MD, A D Politano MD, L M Riccio MD, K A Popovsky RN, Prof R G Sawyer MD)

Correspondence to: Prof Robert G Sawyer, PO Box 800709, 1215 Lee Street, Charlottesville, VA 22901, USA **rws2k@virginia.edu**

Summary

Background Antimicrobial treatment in critically ill patients can either be started as soon as infection is suspected or after objective data confirm an infection. We postulated that delaying antimicrobial treatment of patients with suspected infections in the surgical intensive care unit (SICU) until objective evidence of infection had been obtained would not worsen patient mortality.

Methods We did a 2-year, quasi-experimental, before and after observational cohort study of patients aged 18 years or older who were admitted to the SICU of the University of Virginia (Charlottesville, VA, USA). From Sept 1, 2008, to Aug 31, 2009, aggressive treatment was used: patients suspected of having an infection on the basis of clinical grounds had blood cultures sent and antimicrobial treatment started. From Sept 1, 2009, to Aug 31, 2010, a conservative strategy was used, with antimicrobial treatment started only after objective findings confirmed an infection. Our primary outcome was in-hospital mortality. Analyses were by intention to treat.

Findings Admissions to the SICU for the first and second years were 762 and 721, respectively, with 101 patients with SICU-acquired infections during the aggressive year and 100 patients during the conservative year. Compared with the aggressive approach, the conservative approach was associated with lower all-cause mortality (13/100 [13%] *vs* 27/101 [27%]; p=0·015), more initially appropriate therapy (158/214 [74%] *vs* 144/231 [62%]; p=0·0095), and a shorter mean duration of therapy (12·5 days [SD 10·7] *vs* 17·7 [28·1]; p=0·0080). After adjusting for age, sex, trauma involvement, acute physiology and chronic health evaluation (APACHE) II score, and site of infection, the odds ratio for the risk of mortality in the aggressive therapy group compared with the conservative therapy group was 2·5 (95% CI 1·5–4·0).

Interpretation Waiting for objective data to diagnose infection before treatment with antimicrobial drugs for suspected SICU-acquired infections does not worsen mortality and might be associated with better outcomes and use of antimicrobial drugs.

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Introduction

Until recently, the use of antimicrobial drugs was thought by physicians to be relatively risk free, which resulted in a tendency to give these drugs at the smallest suspicion of infection. However, excessive antimicrobial use is now known to be associated with resistance and other associated effects. Consequently, the decision to start treatment in a possibly (but not certainly) infected critically ill patient is made based on a balance between three considerations: the certainty of the diagnosis,[1–5] the risk of delaying treatment,[6–12] and the environmental damage caused by the use of antimicrobial drugs,[13–25] including the selection of resistant organisms.

Two possibilities for the timing of the start of antimicrobial treatment in critically ill patients exist:[26,27] starting treatment immediately after obtaining cultures, knowing that many uninfected patients will receive unnecessary treatment; or withholding antimicrobial treatment until an infection is confirmed by objective data, knowing that some patients might have potentially harmful delays in treatment. There is no standardised approach to the timing of the start of antimicrobial therapy. We postulated that delaying the administration of broad-spectrum antimicrobial drugs until the initial return of objective evidence of infection would not significantly worsen mortality and would be potentially beneficial in terms of reduction of antimicrobial use and the induction of resistance.

Methods

Study design

Patients aged 18 years or older who were admitted to the University of Virginia (Charlottesville, VA, USA) surgical intensive care unit (SICU) were prospectively followed up until discharge from Sept 1, 2008, to Aug 31, 2010. Patients not on a surgical service and patients with

burns were excluded. The 16-bed SICU at the University of Virginia is managed by five board-certified intensivists. All orders are written by the SICU team, and a clinical pharmacist reviews all drug orders, including antimicrobial drugs. Patients in the SICU are routinely discharged to an immediately contiguous acute care ward.

Because empirical antimicrobial prescribing practices can alter unit-wide rates of infection and isolation of resistant pathogens, we undertook a 24-month, before and after, quasi-experimental study rather than randomising individual patients. The 2-year study period was split into two 1-year periods: one in which an aggressive protocol was used and one in which a conservative protocol was used. This study design allows assessment of unit-wide resistance rates that might be expected if either protocol was implemented elsewhere in a similar intensive care unit (ICU). We chose a 2-year duration to account for seasonal variation.

The study was approved by the University of Virginia Institutional Review Board. The need for informed consent was waived because both treatment methods were in use and were regarded as equivalent and implementation was done as part of protocol-directed care.

Procedures

From Sept 1, 2008, to Aug 31, 2009, the aggressive protocol was used, which stated that patients be treated with an early, aggressive method to the start of antimicrobial treatment for the suspicion of infection after drawing of blood and other relevant cultures. After 72 h of empirical treatment, if blood cultures did not suggest an infection, antimicrobial drugs were stopped. From Sept 1, 2009, to Aug 31, 2010, the conservative protocol was used, in which antimicrobial drugs were withheld until there was microbiological evidence of infection. Antimicrobial treatment was started when there was objective evidence of infection. In the SICU, blood cultures are done for any patient suspected of having an infection without an obvious site, and timing of culture provides a common starting point for future measures. Common triggers for sending blood cultures include fever or other signs of sepsis.

Objective evidence of infection included, for pulmonary infection, more than 100 000 colony forming units (CFU) of bacteria on a quantitative endotracheal suction specimen; for intra-abdominal infections, any pathogen on Gram stain from a sterilely obtained aspirate; for bloodstream infection, any growth; for urinary tract infection, more than 100 000 CFU of a pathogen per mL of urine; and any pathogen on Gram stain of a sterilely obtained aspirate from a normally sterile body cavity. For infections for which diagnosis is routinely made without culture (eg, surgical site infection) the protocol did not have to be followed and antimicrobial drugs were started immediately. We followed the US Centers for Disease Control and Prevention criteria for the definition of infection.[28]

Resistant pathogens were defined as,[29] for Gram-negative pathogens, any organism shown by in-vitro

	Aggressive	Conservative
All ICU admissions		
All patients	762	721
Age (years)	50·1 (18·1)	51·7 (15·8)
Men	457 (60%)	415 (58%)
APACHE II score	18·4 (6·2)	18·5 (6·5)
Diagnosis on admission to the ICU		
Polytrauma	367 (48%)	353 (49%)
Emergency general surgery	181 (24%)	178 (25%)
Decompensation on ward	74 (10%)	65 (9%)
Liver transplantation	66 (9%)	72 (10%)
Intra-abdominal infection*	50 (7%)	42 (6%)
Scheduled postoperative admission	40 (5%)	36 (5%)
Kidney transplantation	20 (3%)	15 (2%)
Vascular surgery	2 (<1%)	14 (2%)
Deaths in the ICU	45 (6%)	32 (4%)
ICU-acquired infections		
Patients with ICU-acquired infections	101 (13%)	100 (14%)
Age (years)	54·1 (16·8)	55·5 (16·8)
Men	66 (65%)	61 (61%)
Hospital LOS (days)	37·6 (27.8)	37·9 (35·4)
LOS after start of antimicrobial treatment (days)	26·3(24·1)	26·8 (29·5)
APACHE II score	18·7 (6·5)	20·5 (6·8)
WBC count (×10^9 cells per L)	15·2 (11·2)	15·3 (7·2)
Ethnic origin		
White	87 (86%)	87 (87%)
Black	10 (10%)	9 (9%)
Hispanic	2 (2%)	3 (3%)
Other	2 (2%)	1 (1%)
Comorbidities		
Diabetes mellitus	21 (21%)	21 (21%)
Cardiac disease	27 (27%)	27 (27%)
Hypertension	33 (33%)	46 (46%)
Vascular disease	4 (4%)	4 (4%)
Cerebrovascular disease	5 (5%)	4 (4%)
Chronic renal insufficiency	6 (6%)	2 (2%)
Haemodialysis	12 (12%)	7 (7%)
Mechanical ventilation	57 (56%)	58 (58%)
Malignancy	4 (4%)	10 (10%)
Chronic liver disease	7 (7%)	6 (6%)
Corticosteroids	18 (18%)	16 (16%)
Dyslipidaemia	6 (6%)	8 (8%)
Previous transfusion	76 (75%)	69 (69%)

Data are number (%) or mean (SD). Patients with isolated head injury are admitted to a separate unit and vascular surgery patients were not routinely admitted to the surgical ICU. APACHE=acute physiology and chronic health evaluation. ICU=intensive care unit. LOS=length of stay. WBC=white blood cell. *Also included in emergency general surgery.

Table 1: **Demographics and baseline characteristics**

	Aggressive (n=247)	Conservative (n=237)	p value
Pneumonia	75 (30%)	93 (39%)	0·040
Bloodstream	49 (20%)	46 (19%)	0·91
Intra-abdominal	31 (13%)	22 (9%)	0·25
Urinary tract	33 (13%)	36 (15%)	0·57
Surgical site	19 (8%)	21 (9%)	0·64
Vascular catheter	14 (6%)	8 (3%)	0·23
Other	26 (11%)	11 (5%)	0·0149

Some percentages do not sum to 100 because of rounding.

Table 2: **Types of infections**

	Aggressive (n=247)	Conservative (n=237)	p value
Most commonly identified organisms			
Enterococcus faecium	27 (11%)	21 (9%)	0·45
Vancomycin-resistant *E faecium*	24 (10%)	18 (8%)	0·41
Pseudomonas aeruginosa	26 (11%)	32 (14%)	0·42
Staphylococcus aureus	26 (11%)	18 (8%)	0·27
MRSA	18 (7%)	4 (2%)	0·0041
Klebsiella pneumoniae	22 (9%)	17 (7%)	0·48
Enterobacter cloacae	21 (9%)	15 (6%)	0·36
Staphylococcus epidermidis	12 (5%)	8 (3%)	0·40
Escherichia coli	10 (4%)	28 (12%)	0·0043
Citrobacter spp	9 (4%)	8 (3%)	0·84
Klebsiella oxytoca	8 (3%)	6 (3%)	0·62
Enterococcus faecalis	7 (3%)	12 (5%)	0·25
Serratia spp	6 (2%)	8 (3%)	0·58
Haemophilus influenzae	5 (2%)	11 (5%)	0·13
Streptococcus spp	4 (2%)	6 (3%)	0·51
Proteus sp	2 (1%)	4 (2%)	0·45
Acinetobacter spp	2 (1%)	6 (3%)	0·15
Other species*			
Candida spp	47 (19%)	33 (14%)	0·17
Clostridium difficile	8 (3%)	3 (1%)	0·15
Resistant organisms			
Gram-negative rods	65 (26%)	84 (35%)	0·030
Gram-positive cocci	40 (16%)	22 (9%)	0·023

*Fungi and microbes that contribute to antibiotic toxicity and environmental damage (*Clostridium difficile*). MRSA=meticillin-resistant *Staphylococcus aureus*.

Table 3: **Presence of Gram-negative and Gram-positive organisms, other species, and resistant organisms**

testing to be resistant to all penicillin and β-lactamase inhibitor combinations, all cephalosporins, all fluoroquinolones, all carbapenems, or all aminoglycosides were deemed resistant; for Gram-positive pathogens, meticillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE) were classed as resistant pathogens.

Patients known to be infected or colonised with MRSA, VRE, Gram-negative bacteria resistant to two or more classes of antimicrobial drugs, or *Clostridium difficile* were treated under contact isolation. Patients otherwise underwent weekly surveillance cultures. Alcohol-based hand rub was used (except for patients with known *C difficile* infection, where soap and water was used) and hand washing was done before and after all patient contact, as per unit protocol. Although we did not monitor them specifically, none of these procedures changed during the 2-year intervention, nor did staffing levels, populations of patients, device use, or other identifiable major methods for the management of patients. As a surgical unit, rapid source control within 2–4 h of diagnosis was routinely done for intra-abdominal infections and soft tissue infections.

Piperacillin/tazobactam and vancomycin were the first-line empirical antimicrobial drugs. De-escalation was done. Carbapenems were reserved for multidrug-resistant organisms.

The primary outcome was in-hospital mortality. Secondary outcomes were length of hospital stay, incidence of ICU-acquired infections, incidence of ICU-acquired infections with resistant pathogens (including fungi and *C difficile*), duration of therapy, time to start of treatment with antimicrobial drugs, and appropriateness of initial and overall antimicrobial therapy. Analyses were by intention to treat; patients were categorised by the period of protocol during which they were treated, and compliance with the protocol was quantified by measuring time from fever (when present) and drawing of blood cultures to start of antimicrobial therapy.

Any patient who was unstable and needed vasoactive drugs after appropriate resuscitation and who was suspected of harbouring an infection could have empirical antimicrobial drugs started immediately at the discretion of the attending intensivist. These patients were nonetheless included in all analyses. Patients with a mean arterial pressure (MAP) of less than 60 mm Hg after volume resuscitation were treated with vasoactive drugs.

Appropriate antimicrobial treatment was defined as use of antimicrobial drugs that were effective against all pathogens eventually isolated from cultures by in-vitro testing, on the basis of review of sensitivity data derived from the specific site of infection after the diagnosis of infection was confirmed. Initial appropriateness was defined as effective treatment given on the first calendar day of treatment. Compliance with an aggressive approach was defined as start of antimicrobial treatment within 12 h of blood culture, based on data from Barie and colleagues[30] that suggested the mean time to start of antimicrobial treatment in survivors of sepsis was 13 h in a similar SICU.

Clinical data were prospectively collected three times per week. The acute physiology and chronic health evaluation (APACHE) II score was calculated at the time of admission and at diagnosis of infection. Mortality included deaths before hospital discharge.

Statistical analysis

We did univariate comparisons: continuous variables with a Gaussian distribution were compared with Student's *t* tests with equal or unequal variance as assessed by *F* tests; continuous variables with a skewed distribution were compared with the Wilcoxon rank sum test. Categorical data were analysed with χ^2 testing or the Fisher's exact test, depending on the sample size. All continuous values are expressed as mean (SD) or median (IQR).

Relative risk of death was calculated, and subsequently mortality risk when adjusted for the a-priori identified variables of APACHE II, trauma involvement, sex, age, and site of infection. Risk of death (odds ratio [OR] with 95% CI) was estimated with a hierarchical generalised linear model to account for over-dispersed variance associated with repeated patient level indicators (eg, one patient with multiple sites of infection). Statistical analyses were done with SAS (version 9.1.3).

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

762 patients were admitted to the ICU during the first year (aggressive approach) of the study, 101 (13%) of whom acquired 247 discrete sites of infection in the ICU. During the second year (conservative approach), 100 (14%) of 721 admitted patients acquired an infection, with 237 sites of infection. The two study groups were balanced for baseline characteristics (table 1). The incidences of infection were similar, with 32·0 infections per 100 admissions and 26·0 infections per 1000 patient-days during the aggressive period versus 32·9 infections per 100 admissions and 27·2 infections per 1000 patient-days during conservative treatment. Table 2 shows the types of infections that were treated.

Table 3 lists the pathogens present in ICU-acquired infections. More resistant Gram-negative organisms were recovered during the conservative period, whereas infections with resistant Gram-positive pathogens were about twice as common during the aggressive period. Although mortality after resistant Gram-positive infection was similar between the two groups (21 of 40 [53%] in the aggressive phase, 10 of 22 [46%] in the conservative phase, p=0·6) mortality after infection with a resistant Gram-negative organism was higher during the aggressive period (37 of 65 [57%]) than during the conservative period (28 of 84 [33%]; p=0·004). No specific outbreaks that needed changes in infection control measures (which were consistent throughout the study) were noted during the study.

Table 4 lists the time from blood culture and fever to start of treatment and shows that there was a significant delay in time to treatment during the conservative treatment year as well as a shorter duration of therapy compared with the aggressive treatment. Most patients were ultimately treated with appropriate antimicrobial drugs, and most of those who were not died before the availability of final culture results (six patients died before culture results were available, all were in the aggressive group). Initial

	Aggressive (n=247)	Conservative (n=237)	p value
Time from blood culture to start of treatment (h)			
Number	189	206	
Mean (SE)	20·9 (24·4)	34·8 (34·4)	<0·0001
Median (IQR)	12 (3–30)	22 (7–58)	<0·0001
Time from fever to start of treatment (h)			
Number	103	139	
Mean (SD)	11·1 (14·9)	35·2 (37·4)	<0·0001
Median (IQR)	6 (3–14)	24 (9–44)	<0·0001
Duration of antimicrobial treatment (days)			
Mean (SD)	17·7 (28·1)	12·5 (10·7)	<0·008
Median (IQR)	11 (7–8)	10 (7–14)	0·015
Appropriate antimicrobials (number [%])			
Initial*	144 (62%)	158 (74%)	0·0095
Switched	64 (28%)	48 (23·5%)	0·17
Overall	208 (90%)	206 (96%)	0·010

Not all patients had blood cultures drawn or had fever (temperature ≥38·5°C). Antibiotics were generally switched to appropriate coverage 3 days after cultures were sent when sensitivities returned. *Data for appropriate initial therapy were available from 214 patients in the aggressive group, and 231 in the conservative group.

Table 4: **Time to start of treatment and appropriateness of antibiotic therapy**

	Aggressive (n=247)	Conservative (n=237)	p value
Pneumonia	23/75 (31%)	15/93 (16%)	0·077
Bloodstream	19/49 (39%)	15/46 (33%)	0·67
Intra-abdominal	13/31 (42%)	6/22 (27%)	0·24
Urinary tract	14/33 (42%)	5/36 (14%)	0·045
Surgical site	12/19 (63%)	4/21 (19%)	0·062
Vascular catheter	6/14 (43%)	4/8 (50%)	0·84
Other	12/26 (46%)	1/11 (9%)	0·0309

Data are n/N (%).

Table 5: **Patient mortality by site of infection**

	Aggressive (n=27)	Conservative (n=13)	p value
Death while receiving antimicrobials	20 (74%)	8 (62%)	0·66
Death due to infection	14 (52%)	7 (54%)	1·00
Death due to underlying pathology	10 (37%)	6 (46%)	0·84
Death due to new onset, non-infectious disorder	2 (7%)	0 (0%)	0·82
Multifactorial death	1 (4%)	0 (0%)	1·00

Table 6: **Causes of death while receiving antimicrobials**

	Univariate comparison p value	F statistic	F statistic p value	OR (95% CI)
Trauma (yes vs no)	<0·0001	26·7	<0·0001	0·2 (0·1–0·4)
APACHE II score	..	24·1	<0·0001	1·1 (1·1–1·2)
Aggressive vs conservative treatment	<0·0001	14·8	0·0001	2·5 (1·5–4·0)
Women vs men	0·0049	12·7	0·0004	2·4 (1·4–3·9)
Age	..	10·4	0·0014	1·0 (1·0–1·0)
Site				
Intra-abdominal vs pneumonia	0·39	3·1	0·88	1·0 (0·5–2·2)
Bloodstream vs pneumonia	0·24	..	..	1·3 (0·7–2·5)
Urinary tract vs pneumonia	0·53	..	..	0·8 (0·4–1·8)
Surgical site vs pneumonia	0·19	..	..	1·6 (0·3–10·4)
Central catheter vs pneumonia	0·13	..	..	1·4 (0·5–4·1)

Univariate analyses of predictors are displayed. All variables were identified a priori and included in the model even when not statistically significant on univariate analysis.

Table 7: **Hierarchical generalised linear model for predictors of mortality**

	Aggressive	Conservative	p value
Lowest MAP mm Hg			
All patients	247	237	
Mean (SD)	75·9 (26·6)	68·9 (25·0)	<0·0001
Median (IQR)	65 (56–90)	62 (54–68)	<0·0001
Deceased patients	27 (11%)	13 (5%)	
Mean (SD)	66·2 (25·9)	71·9 (58·0)	<0·0001
Median (IQR)	69 (61–110)	63 (56–90)	<0·0001
Infections associated with MAP <60 mm Hg			
Number	95	110	0·077
APACHE II score			
Mean (SD)	22·0 (6·9)	22·4 (6·4)	0·71
Median (IQR)	21 (17–29)	22 (17–27)	0·79
Time from blood culture to initiation of treatment (h)			
Mean (SD)	9·2 (14·0)	31·8 (37·6)	<0·0001
Median (IQR)	4 (3–12·5)	20 (8–39)	<0·0001
Deaths	63 (66%)	29 (26%)	0·0004

MAP=mean arterial pressure.

Table 8: **Distribution of mean arterial pressures and descriptive statistics and outcomes for infections treated with MAP less than 60 mm Hg**

antimicrobial therapy improved significantly during conservative treatment. The most common pathogens recovered from patients without appropriate initial empirical therapy were *Candida* spp (n=38), VRE (n=24), and resistant *Pseudomonas aeruginosa* (n=19). During the aggressive period, 151 (23%) of 661 patients never diagnosed with an ICU-acquired infection were started on antimicrobial treatment for suspicion of infection; 97 (64%) had their antimicrobial drugs discontinued by 3 days and 21 (14%) subsequently died in the ICU. During the conservative period, 31 (5%) of 621 patients never diagnosed with an ICU-acquired infection were started on antimicrobial drugs; 17 (55%) had their antimicrobial drugs stopped by 3 days and four (13%) died in the ICU.

99 (40%) of 247 patients with ICU-acquired infections (all sites) died in the aggressive treatment group compared with 50 (21%) of 237 in the conservative period (p<0·0001). This translated into 27 (27%) of 101 deaths among patients who acquired an infection in the ICU during the aggressive period compared with 13 (13%) of 100 deaths during the conservative period (p<0·015), with a relative risk of death in the aggressive period of 2·1 (95% CI 1·2–3·8). Table 5 lists mortality according to site of infection. Table 6 shows the investigator-assessed causes of death for patients with ICU-acquired infections—no significant differences were noted between groups.

Trauma involvement, APACHE II score, and treatment protocol (aggressive *vs* conservative) were the most important determinants of mortality (table 7). Aggressive treatment generated an adjusted OR of death of 2·5 (95% CI 1·5–4·0) when individual infections were studied. In a separate model where individual patients rather than infections were included, the adjusted OR for death during the aggressive period was 4·0 overall (95% CI 1·6–9·8).

Table 8 lists the lowest MAP within 24 h of the start of treatment for each treatment cohort for all patients and those who died. Data specifically for patients with a MAP less than 60 mm Hg at the time of the start of treatment of infection and treated with vasoactive drugs (most commonly norepinephrine) are also given and show that the results are similar to the entire cohort—ie, ICU-acquired infections treated during the conservative period were associated with a lower mortality despite a delayed start of antimicrobial use.

Discussion

It is challenging to correctly time the start of antimicrobial treatment in patients who are critically ill. First, patients often exhibit signs and symptoms of infection that are the consequence of non-infectious causes.[29] Second, the diagnosis of infection still generally depends upon the growth of pathogens from culture over 48–72 h. In our study, we showed that patients managed under an aggressive treatment protocol had a more rapid start of treatment, a lower chance of receiving initially appropriate treatment, a prolonged duration of antimicrobial treatment, and significantly lower survival (panel).

Most published observational data suggest that the time to the administration of appropriate antimicrobial drugs is a major determinant of outcome. Ibrahim and colleagues[7] reported a 2·2-times increased mortality in patients with bloodstream infections when appropriate antimicrobial drugs were delayed, and Barie and colleagues[30] suggested a 2·1% increase in mortality for every 30 min delay in appropriate antimicrobial initiation for patients in an ICU. Although valuable, these data were not obtained in a prospective manner and did not specifically assess triggers for the start of treatment. The

absence of concise criteria for the start of antimicrobial treatment in these observational studies, particularly where ICU-acquired pneumonia—with its problematic diagnosis—is the most common infection, might partly explain the discordance with our findings.

Several plausible reasons exist for why waiting to start antimicrobial treatment until confirmation of infection was associated with improved survival. First, the rate of adequacy of initial treatment was higher in the conservative group, most probably because the first-line antimicrobial regimen was piperacillin/tazobactam and vancomycin and the most common pathogens isolated in cases of inappropriate initial therapy, *Candida* spp and VRE, are not treated with this regimen. Conversely, when antimicrobial selection was delayed, the finding of yeast forms or Gram-positive cocci often prompted immediate treatment with antifungal or VRE drugs and initially appropriate therapy.

Second, the duration of antimicrobial treatment was significantly longer when an aggressive approach to the start of antimicrobial treatment was used, which perhaps caused collateral damage and decreased survival. There are several reasons for the over-long course of antimicrobial treatment. Ineffective antimicrobial drugs were more commonly used during the period of aggressive antimicrobial use. Also, the protocol label of aggressive might have been misinterpreted to include more antimicrobial treatment. Our hypothesis is that the microbiomic damage caused by 48–72 h of ineffective antimicrobial drugs at the start of treatment, with perhaps a subsequent 48–72 h of unnecessary antimicrobial therapy at the end of treatment, outweighs any benefit of starting treatment before microbiological confirmation of infection.

Third, experience gained during the aggressive year might have resulted in an improved ability of clinicians to recognise, diagnose, and treat infections, although such behaviour is difficult to measure. Finally, the protocol used during the aggressive period implied that all patients with signs or symptoms of infection, including fever or leucocytosis, needed antimicrobial therapy because cultures were routinely pending on these patients. Therefore, treatment was prolonged in some patients because they continued to have a residual leucocytosis or fever at the time that antimicrobial drugs should have been stopped.

Several study weaknesses deserve discussion. First, the trial was not randomised. Randomisation was deemed problematic because one of the main secondary outcomes was the effect of the protocols on the rates of infection with resistant pathogens—the reasoning being that the more conservative period might be associated with less antimicrobial use and an overall decline in resistance. Because our data suggest no consistent changes in resistance patterns with either method (more resistant Gram-positive infections were noted during the aggressive period and more resistant Gram-negative infections during the conservative period), a randomised approach now seems more feasible.

Second, our study was undertaken at one centre and the number of patients included was low. Repetition in a much larger, multicentre format, with either a patient or cluster randomised design, will be necessary before the conservative strategy can be widely adopted. Similarly, the findings cannot be extrapolated to other populations of critically ill patients, including those in medical or paediatric ICUs.

Third, as noted earlier, we did not show a clearly positive effect on resistance rates with the more conservative antimicrobial use strategy, although Gram-negative resistance did not seem to be associated with mortality, which is similar to our previous findings.[29]

Fourth, our data give no treatment suggestions for patients who are persistently septic but have negative cultures, especially while receiving empirical antimicrobial drugs. Finally, compliance with the protocol was imperfect, because the median time from blood culture to antimicrobial administration was 12 h, even in the aggressive group. However, these results are probably representative of what can be expected when such a protocol is introduced to an ICU and correspond with the mean of 17 h reported in the study by Barie and colleagues.[30]

In conclusion, there is no evidence that starting antimicrobial drugs as soon as an infection is suspected

Panel: Research in context

Systematic review

We searched PubMed and Ovid with the terms "critical care" and "empiric antibiotic", which returned about 180 articles, none of which answered the question of appropriate timing for the start of antimicrobial treatment in critically ill, infected patients. Several articles reported difficulties in establishing the diagnosis of infection since similar signs and symptoms of infection are exhibited in patients with non-infectious causes,[1-3] the diagnosis of infection still depends upon growth of pathogens from culture, and there is an absence of accepted gold standards for diagnosis of infections.[4,5] Early, empirical initiation of antibiotics affects the ultimate survival of the patient,[6-12] although broad use of antimicrobial drugs is a known risk factor for induction of resistance among common pathogens.[13-18,29] As a result, researchers have suggested different strategies that would balance administration of antibiotics in the ICU with the potential harmful effects to the patient and the unit flora, such as restriction of specific antibiotic classes, limited formularies, early cessation of treatment on the basis of clinical response, de-escalation of antibiotics when possible,[6] and use of strict antibiotic use protocols and guidelines (additional references for relevant studies are provided in the appendix). However, more accurate timing of antibiotic administration has never been addressed.

Interpretation

Our findings suggest that in haemodynamically stable surgical patients with critical illness who are suspected of having an infection, waiting for objective evidence of infection before starting empirical treatment does not seem to worsen outcomes. Future research needs to focus on examining similar interventions in a multicentre trial of surgical patients, as well as smaller exploratory studies in medical and non-surgical adult and paediatric populations. Before confirmation, our findings should change medical practice only when the change can be done in a closely monitored situation where outcomes are rigorously and frequently analysed.

See Online for appendix

is beneficial. Initiation of antimicrobial treatment is easy; however, cessation of therapy has become a difficult task. Although additional studies need to be done to identify optimum use of these drugs in terms of spectrum, duration, diagnostic precision, and patient population, our data suggest that waiting until infection is confirmed might be at least an equivalent option to a more aggressive approach where antimicrobial treatment is begun when infection is merely suspected.

Contributors

TH was involved in the data collection, study design, data analysis, data interpretation, search of published work, and critical review. LHR was involved in the data collection, writing, search of published work, and critical review. BRS was involved in the data analysis, data collection, and critical review. RM was involved in the data collection, writing, and critical review. TRF was involved in the data analysis, data collection, writing, search of published work, and critical review. ADP was involved in the data collection, search of published work, and critical review. LMR was involved in the data collection, search of published work, and critical review. KAP was involved in the data collection and critical review. RGS was involved in the data collection, study design, data interpretation, writing, search of published work, and critical review.

Conflicts of interest

We declare that we have no conflicts of interest.

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Antibiotics for surgical patients: the faster the better?

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Intensive-care units (ICUs) are often described by microbiologists as genesis units for selection, maintenance, and transmission of antibiotic resistance in hospitals. In such units, antibiotic use is often several times higher than in general wards,[1] and opportunities for transmission of resistance between patients are common. Efforts to control antibiotic resistance in hospitals often centre on ICUs, with interventions such as admission screening for meticillin-resistant *Staphylococcus aureus* (MRSA)[2] and antibiotic stewardship.[3]

Despite this high antibiotic use, and much research into new treatments, mortality for patients with infections in ICUs remains high.[4,5] Several studies have shown improved outcomes, particularly mortality, with rapid administration of antibiotics. However, this effect has not been identified in all studies and the importance of rapid administration probably varies with type of infection and severity of illness. Inconsistent outcomes might also be related to study design, size, and setting. Source control and early appropriate antibiotic therapy are regarded as key for best outcomes.[5,6]

In *The Lancet Infectious Diseases*, Tjasa Hranjec and colleagues[7] present data for early and delayed treatment of infections arising within a surgical ICU. The results of their study challenge conventional wisdom: patients who received antibiotics earlier and before culture results became available (from Sept 1, 2008, to Aug 31, 2009; n=762, 101 infections) seemed to have a higher mortality than patients managed with treatment delayed until after microbiology results became available (from Sept 1, 2009, to Aug 31, 2010; n=721, 100 infections). Unadjusted mortality was two-times higher for early administration than for delayed treatment, giving a number need to harm of seven—a very important result if confirmed. Multivariable analysis confirmed an odds ratio for death of 2·5 (95% CI 1·5–4·0). Thus, not only was there no benefit of early antibiotic administration, but early treatment was also associated with a 13% increase in mortality.

The investigators acknowledge limitations of their single-centre, two-period, unblinded, observational study—only associations can be inferred from such a study design, not causality.[8] Other aspects of this study should likewise caution against immediate widespread application of their approach. Both groups of patients received prolonged antibiotic therapy (12–17 days), which has been associated with adverse outcomes in other studies.[9,10] Also, the appropriateness of antibiotic seems low by comparison with other studies. Initial antibiotic therapy was only appropriate in 62–74% of patients compared with 84% in a recent multicentre trial in sepsis.[11] Administration of antibiotics seemed slow when compared with targets for antibiotic administration in emergency departments. The Surviving Sepsis Campaign recommends that "intravenous antibiotic therapy should be started within the first hour of recognition of severe sepsis, after appropriate cultures have been obtained".[6] In Hranjec and colleagues' study, even the early treatment group only received antibiotics a mean of 11 h (SD 14·9) after fever was identified and 21 h (37·4) after blood cultures were taken, so the practices used might not be applicable in other settings.

Additionally, Hranjec and colleagues provide few details about control measures that could explain the changing epidemiology of MRSA and vancomycin-resistant enterococci (both much higher in year 1 and well known to have higher mortality) versus resistant Gram negative organisms (higher in year 2 and where mortality was reduced). Improved control of MRSA is well described in many US hospitals during the study period.[12] Also, the excess total mortality in year 1 (47) versus year 2 (21) is not explained, nor differences in underlying diseases and diagnosed infections, which might have been clinically significant in view of the small numbers and differences in outcome. Interrupted time-series analysis might have helped provide a better understanding of some of this data.

We await studies with a more robust design, which hopefully will confirm the results of this study and provide welcome relief from the seemingly ever increasing tendency to spiralling therapeutic empiricism. In the meantime, rapidly administered, well-designed empiric treatment based on local epidemiology must remain the norm for patients with sepsis and hypotension. In the UK, daily joint ICU ward-rounds with a microbiologist are common. Patients who are not hypotensive can usually await initial Gram stain results to confirm or refute the presence of infection. Biomarkers such as C-reactive protein can often help in the crucial decision-making process.[13]

Antibiotic resistance is epidemic and the development of new drugs has stalled, thus the medical community must now be more critical than ever of present antibiotic use, and in this context, the study by Hranjec and colleagues is to be applauded.

*David W Noble, *Ian M Gould*
Aberdeen Royal Infirmary, Aberdeen AB25 2ZN, UK
i.m.gould@abdn.ac.uk

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Cross-protection is crucial for prophylactic HPV vaccination

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In *The Lancet Infectious Diseases*, Talia Malagón and colleagues[1] did a systematic review and comparison of cross-protective efficacy induced by the two licensed human papillomavirus (HPV) vaccines. Malagón and colleagues reported differences in the cross-protection against HPV types 31, 33, and 45—the bivalent vaccine yielded better protection against persistent infections with these three high-risk types and associated cervical intraepithelial neoplasia (CIN) grade 2 or worse.

In the context of bivalent versus quadrivalent HPV vaccines and their induced cross-protection against non-vaccine HPV types, not only the different adjuvant systems deserve comment but also different expression vectors and post-translational cleavage of the L1 protein in yeast versus eukaryotic cells. Induced cross-protection is related to the full or reinforced exploitation of T-helper and memory B cells, and, especially for B cells, the differential availability of the type-common epitopes might make the difference. T-helper cells seem to be lacking in some individuals infected with HPV 16, as suggested by presence of low avidity HPV 16 antibodies and associated susceptibility to infections with other (low-risk) HPV types in a proportion of sexually active women.[2] Whether or not antibody avidity (a surrogate of appropriate T-helper cells and success of other immunisations) matures in all HPV-vaccinated individuals warrants further investigation.[3] Furthermore, detailed studies enabling comparison of monoclonal antibody-based epitope maps[4] with the three-dimensional structure of the high-risk HPV L1 proteins[5] have not been fully exploited.[6] Immunobiology of HPV-vaccine-induced (neutralising) antibody response might eventually need to be studied epitope by epitope.

Differential protective effect of vaccination on HPV 31, 33, and 45 exposure and challenge compared with HPV 16 and 18 challenge after trial enrolment was assessed by the Malagón and colleagues.[1] HPV 16 is the most prevalent high-risk HPV type and could be the most common high-risk HPV infection after sexual debut. High prevalence of HPV 16 means that for HPV 16 and 18 or HPV 6, 11, 16, and 18 vaccination of young adults already infected with HPV 16, B cell clones crucial for the cross-protective immune response might have been lost in these individuals. On the contrary, in adolescents who are vaccinated early, the best possible repertoire of naive B cells is available for establishing the widest cross-protective immune response by vaccination. Differencial loss of memory B cells cannot be tackled simply by comparing baseline