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ORIGINAL ARTICLE

Adherence to recommended care for antibiotic use in ICU patients: a retrospective case record study

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Abstract

Background: The burden of antimicrobial resistance in healthcare settings is especially prevalent at the intensive care unit (ICU). It is important that physicians and nurses appropriately use antibiotics and adhere to antibiotic use recommendations to conserve currently available antibiotics.

Methods: A retrospective analysis of patients' medical and nursing records was conducted to study the adherence to recommendations that define appropriate antibiotic use. Two sets of quality indicators were studied in the ICU of a large non university teaching hospital in the Netherlands:[1] quality indicators for appropriate antibiotic use at the ICU, and[2] quality indicators on Selective Digestive tract Decontamination (SDD).

Results: A total of 150 patients were included. The highest adherence rate was found for the recommendation 'stop third generation cephalosporin therapy as part of SDD after four days' (44/46; 95.7%). Attention should be paid to doubling the dose of oral and enteral SDD if so required by protocol, as professionals adhered to this recommendation in only 26.3% of the patients (10/38).

Conclusions: The quality indicators applied in this study can be used by hospital antibiotic stewardship teams to determine where to set priorities to improve antibiotic use in ICU patients. More research in other ICUs is needed to gain better insight into the adherence to recommended antibiotic use in daily practice. In a next step, stewardship teams should gain insight into the barriers and facilitators that influence recommended use. Such information is important to develop effective interventions.

Introduction

Antimicrobial resistance (AMR) is a serious threat to patients in all healthcare settings.[1,2] The burden of AMR is especially prevalent in the intensive care unit (ICU), due to prevailing severe infections, excessive antibiotic use, loss of physiological barriers, and high transmission risks between patients.[3-6] Thus, it is crucial to use antibiotics appropriately to prevent or treat infections in the ICU.[7-9]

Quality indicators can be used to measure whether antibiotic use in the ICU is in accordance with recommendations.[10-12] Since 1996, the Dutch National Intensive Care Evaluation Foundation (NICE) registry supports participating ICUs to quantify, compare and improve the quality of care they offer by providing benchmark information.[13,14] The Dutch Society of Intensive Care (NVIC) recently developed a set of quality indicators for appropriate antibiotic use in ICU patients following a modified RAND procedure for the NICE registry.[15,16]

Selective digestive tract decontamination (SDD) has been proven to prevent ICU-acquired infections and reduce mortality rates of patients on mechanical ventilation.[17-19] SDD is a prophylactic strategy that uses antibiotics to prevent severe infections and mortality of critically ill patients on mechanical ventilation.[17-19] SDD in the ICU consists of three interventions: 1) the administration of non-absorbable antibiotics four times daily as oral paste and enteral suspension for the gastrointestinal

tract, 2) the administration of a third-generation cephalosporin therapy in an IV formulation (ceftriaxone or cefotaxime) for a maximum of four days, and 3) the performance of twice weekly surveillance cultures of the throat, perineum, and respiratory tract in order to monitor its effectiveness.[20,21] The Dutch Working Party on Antibiotic Policy (SWAB) guideline recommends to closely monitor SDD in ICUs.[22]

It is unclear to what extent ICUs comply with the quality indicators for antibiotic use developed by the NVIC and SWAB. Therefore, this study aims to measure the adherence of physicians and nurses to antibiotic use recommendations in ICU patients.

Materials and methods

Setting

This study was performed in one non-university teaching hospital located in Nijmegen, the Netherlands. This teaching hospital is part of the 27 top clinical hospitals of the Netherlands and hosts 600 beds. The ICU has a capacity of 14 beds. In 2015, the median length of stay (LOS) in the ICU was 1.6 days, the median duration of mechanical ventilation was 1.2 days, the percentage of ICU re-admissions was 4.8%, and the overall crude mortality rate of patients admitted to the ICU was 7.5%. These numbers are similar to those of a group of comparable ICUs in the Netherlands: in 2015 the median LOS was 1.2 days, the median duration of mechanical ventilation was 1.2 days, the national percentage of readmissions was 5.2%, and the mortality rate was 9.5%.

Patient study population

Patients were included if they were admitted to the ICU and if they fulfilled one of the following two inclusion criteria: patients with a clinically suspected or confirmed infection requiring antibiotic therapy and patients on mechanical ventilation (likely for more than 48 hours) and –thus– requiring SDD. This resulted in three groups: patients with only a suspected or confirmed infection, patients with a suspected or confirmed infection and receiving SDD, and non-infected patients receiving only SDD. Patients already receiving antibiotics before entering the ICU were included if the antibiotic therapy was started within 24 hours before ICU admission and was continued during the ICU stay.

Quality indicators and data collection

There are five NICE and six SWAB quality indicators that define appropriate antibiotic use in ICU patients, described in detail in *table 1*. To obtain a representative sample of patients, retrospective consecutive sampling was performed between January 2016 and April 2017. NICE indicator 1 'quantitative antibiotic use' was defined as days of therapy: total amount of days of therapy in an ICU per 100 patient-days or 100 admissions to an ICU (*table 1*). To assess NICE indicator 1 ('quantitative antibiotic use', see *table 1*), we used crude hospital pharmacy data from January 2013 until January 2017.

The adherence to the remaining recommendations for antibiotic use was measured with quality indicators using a specifically developed algorithm. All data to compute the quality indicators were extracted in a uniform way and entered into a database anonymously. For each patient the date and time of administration of antibiotic therapy, blood cultures, blood concentration levels, surveillance and colonisation cultures and the administration of oral paste and enteral suspension were collected. Further, information on several baseline demographics for the patients was extracted: gender, age, LOS, mortality rate, reason for admission, and the Acute Physiology And Chronic Health Evaluation (APACHE) IV score. One researcher (BW) extracted the data from the following three sources: paper-based medical records, paper-based nursing records, and electronic health records (Mirador® medical software).

Prior to data collection, ten medical records were screened to test whether all the necessary data for the developed algorithms were extracted, whereas definitions were adapted if necessary.

Observations

In addition to the analysis of patient records, 30 live observations were performed over a period of two weeks by two researchers (JS and BW). These observations were performed, because the algorithm evaluating the administration of SDD medication (SWAB indicator 5 and 6) was considered extremely strict. In paper-based nursing records, formally, two signatures are required before each SDD oral paste and each enteral suspension can be regarded as 'administered': the first signature by the attending nurse (when the SDD is prepared) and the second signature by another nurse to double check the type and dose of medication. In the algorithm less than two signatures was interpreted as non-adherent to administration of SDD medication, while two signatures were considered as full adherence. Only the signatures were registered in this study and not the actual administration of SDD medication, which could result in under-evaluation of performance. To correct for possible under-evaluation of performance, live observations were performed. Adherence was considered appropriate when nurses adhered to the following four steps: 1) prepare SDD medication, 2) first signature, 3) second signature, and 4) administering SDD medication. Nurses were informed that with the observations the researchers were trying to gain general insight into preparing and administering procedures in the ICU, not focused on SDD, which is regularly done by pharmacy personnel.

Patient data were anonymised using a unique code. Only the main researcher (BW) had access to the key of this code. The procedures followed were in accordance with the ethical standards on non-medical-scientific research involving humans and approved by the Ethics Committee at the hospital.

Data analysis

We performed descriptive analyses. Adherence to recommen-

Table 1. Quality indicators

Quality indicators	Definition	Numerator	Denominator	Target value
NICE quality indicators				
1) Quantitative antibiotic use	Total antibiotic use in an ICU expressed in days of therapy (DOT) per 100 patient-days or per 100 admissions, whereas one DOT represents the administration of a single agent on a given day regardless of the number of doses administered or dosage strength	Total amount of days of therapy (DOT) in an ICU	100 patient-days or 100 admissions in an ICU	As low as possible
2) Perform blood cultures at the start of antibiotic therapy	Percentage of patients in whom at least two sets of blood cultures were performed before or at the start of empiric, systematic therapy in an ICU	Number of patients in whom at least two sets of blood cultures were performed 24 hours before until 24 hours after systematic antibiotic therapy was started in an ICU	Total number of patients who started systemic antibiotic therapy in an ICU	100%
3) Determine blood levels in time when TDM is indicated	Percentage of patients in whom blood levels were determined in time (within 48 hours) when TDM was indicated in an ICU, whereas an indication for TDM (vancomycin, aminoglycoside or voriconazole)	Number of patients in whom blood levels were determined within 48 hours after the start of antibiotic therapy (vancomycin, aminoglycoside or voriconazole) in an ICU	Total number of patients who received antibiotic therapy (vancomycin, aminoglycoside or voriconazole) for at least 48 hours and in whom TDM was indicated in an ICU	100%
4) Obtain surveillance cultures when SDD is applied	Percentage of patients in whom at least one surveillance culture was obtained of the throat, perineum, and respiratory tract on resistant gram-negative bacteria if SDD had been applied in an ICU	Number of patients in whom at least one surveillance culture was obtained from the throat, perineum, and respiratory tract when SDD was applied in an ICU	Total number of patients in whom SDD was applied in an ICU	100%
5) Number of annual meetings on resistance rates and trends	Number of annual face-to-face meetings between ICU staff and microbiology staff, in which the resistance rates and trends in an ICU population are discussed			At least twice per year
SWAB quality indicators (source Guideline SDD)				
1) Obtain colonisation cultures in time	Percentage of patients in whom the first colonisation cultures were obtained of the throat, perineum, and respiratory tract on gram-negative bacteria within 48 hours after the start of mechanical ventilation in an ICU	Total number of patients in whom colonisation cultures were obtained of the throat, perineum, and respiratory tract on gram-negative bacteria within 48 hours after the start of mechanical ventilation in an ICU	Total number of patients in whom SDD was applied in an ICU	100%
2) Obtain two colonisation cultures per week	Percentage of patients in whom at least two sets of colonisation cultures were obtained per week of the throat, perineum, and respiratory tract on gram-negative bacteria during an episode of mechanical ventilation in an ICU	Total number of patients in whom at least two sets of colonisation cultures were obtained per week of the throat, perineum, and respiratory tract on gram-negative bacteria during an episode of mechanical ventilation in an ICU	Total number of patients in whom SDD was applied in an ICU	100%
3) Doubling of SDD dose if required by protocol	Percentage of patients in whom the dose of SDD was doubled when one of the colonisation cultures of the throat, perineum or respiratory tract grows gram negative microorganisms after the second colonisation culture in an ICU	Total number of patients in whom the dose of SDD was doubled when one of the colonisation cultures of the throat, perineum or respiratory tract grows gram negative microorganisms (Enterobacteriaceae) after the second colonisation culture in an ICU	Total number of patients in whom SDD was applied in an ICU and where the colonisation cultures grows gram negative microorganisms (Enterobacteriaceae)	100%
4) Stop third-generation cephalosporin therapy as part of SDD after four days	Percentage of patients in whom third-generation cephalosporin therapy as part of SDD (ceftriaxone or cefotaxime) was stopped after four days	Total number of patients in whom third-generation cephalosporin therapy as part of SDD (ceftriaxone or cefotaxime) was stopped after four days during ICU admission	Total number of patients who received third-generation cephalosporin therapy as part of SDD (ceftriaxone or cefotaxime) in an ICU	100%
5) Appropriate administration of oral SDD paste	Percentage of patients in whom oral SDD was given four times daily during an episode of mechanical ventilation when SDD was applied in an ICU	Total number of patients in whom oral SDD was given four times daily during an episode of mechanical ventilation in an ICU	Total number of patients in whom SDD was applied in an ICU	100%
6) Appropriate administration of enteral SDD	Percentage of patients in whom enteral SDD was given four times daily during an episode of mechanical ventilation when SDD was applied in an ICU	Total number of patients in whom enteral SDD was given four times daily during an episode of mechanical ventilation in an ICU	Total number of patients in whom SDD was applied in an ICU	100%

dations for antibiotic use was expressed as a percentage of compliance: the number of patients for whom the recommendation was complied with (n) divided by the total number of patients for whom the recommendation was applicable (N) * 100. The recommendations for antibiotic use do not apply to all included patients, resulting in varying sample sizes (e.g. only a few patients in this study had an indication for therapeutic drug monitoring (TDM)). NICE quality indicator 1 'quantitative antibiotic use' was measured for all patients admitted to the ICU receiving antibiotic therapy in the ICU over one year. The indicator was expressed in days of therapy per 100 patient-days and per 100 admissions. We performed all analyses using SPSS V.20.0.

Results

Patient population

We included 150 retrospectively collected patient records based on the inclusion criteria *(figure 1)*. The total study population consisted of three groups: 1) patients with only a suspected or confirmed infection (n=84; 56%, to whom only the NICE quality indicators apply), 2) patients with a suspected or confirmed infection and receiving SDD (n=42; 28%, to whom both sets of quality indicators apply), and 3) non-infected patients receiving only SDD (n=24; 16%, to whom only the SWAB indicators apply). There were no baseline differences between these three groups. Patient characteristics are described in *table 2*.

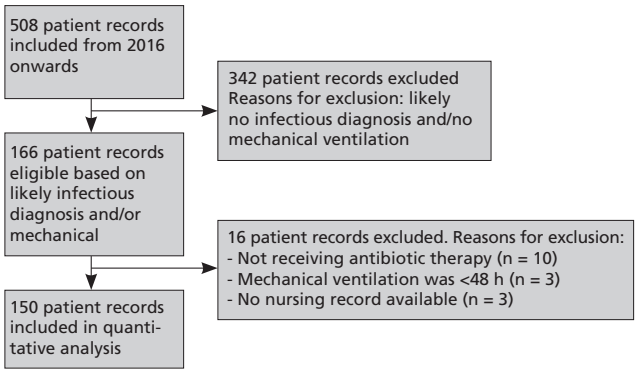

Figure 1. Patient selection

Table 2. Baseline characteristics of the patients

Baseline characteristics	n = 150
Gender, female	58 (38.7)
Age, mean (SD)	67.8 (12.3)
Mechanical ventilation	66 (44)
APACHE IV diagnosis (five most common)	
Pneumonia	54 (36)
Abdominal sepsis	32 (21.3)
Renal infection	15 (10)
Emphysema/bronchitis	13 (8.7)
Cardiovascular disease	11 (7.3)
Length of ICU stay, median (range)	3.5 (0.04-48.7)
Length of hospital stay, median (range)	14.5 (0.3-113.3)
Mortality rate at ICU	22 (14.7)
APACHE IV score, median (range)	69 (18-175)

Numbers are n (%) unless otherwise indicated. SD = standard deviation

Quality indicator scores

Table 3 shows the results on quantitative antibiotic use (NICE indicator 1). The adherence to the remaining antibiotic use recommendations is shown in *table 4*.

Table 3. Quantitative antibiotic use in the ICU per 100 patient-days and per 100 admissions

Year	DOT (including SSD)	Total	DOT (excluding SSD)	Total
Per 100 patient-days				
2016	7338/3562 *100	206	3662/3562 *100	102.8
2015	8635/3927 *100	219.9	4067/3927 *100	103.6
2014	7944/3998 *100	198.7	3867/3998 *100	96.7
2013	7916/3367 *100	235.1	4017/3367 *100	119.3
Per 100 admissions				
2016	7338/982 *100	747.3	3662/982 *100	372.9
2015	8635/982 *100	879.3	4067/982 *100	414.2
2014	7944/994 *100	799.2	3867/994 *100	389
2013	7916/594 *100	1332.7	4017/594 *100	676.3

The ICU and Medium Care were merged in 2014. DOT = days of therapy; SSD = selective digestive tract decontamination

Table 4. Adherence to antibiotic use recommendations

NICE quality indicators	n/N	Adherence, %
2) Perform blood cultures at the start of antibiotic therapy	95/126	75.4
3) Determine blood levels in time when TDM is indicated	08/11	72.7
4) Obtain surveillance cultures when SDD is applied	61/66	92.4
5) Number of annual meetings on resistance rates and trends	4 meetings per year	
SWAB quality indicators	**n/N**	**Adherence, %**
1) Obtain colonisation cultures in time	59/66	89.4
2) Obtain two colonisation cultures per week	44/66	66.7
3) Doubling of SDD dose if required by protocol	10/38	26.3
4) Stop third-generation cephalosporin therapy as part of SDD after four days	44/46	95.7
5) Administration of oral SDD paste	33/66	50*
6) Administration of enteral SDD	30/66	45.5*

*Under evaluation of performance. TMD = therapeutic drug monitoring, SDD = selective digestive tract decontamination

Adherence scores to antibiotic use recommendations

In 95 out of 126 patients (75.4%) two sets of blood cultures were performed within 24 hours after admission (NICE indicator 2). In 8 out of 11 patients (72.7%), physicians and nurses determined the blood levels in time when TDM was indicated (NICE indicator 3). For this indicator, only patients receiving vancomycin, aminoglycosides or voriconazole for at least 48 hours were included, resulting in a study sample of 11 patients, where 9 patients received vancomycin and 2 patients received voriconazole.

In 61 out of 66 patients (92.4%) one surveillance culture of the throat, perineum, and respiratory tract was taken when SDD was applied (NICE indicator 4). In 59 out of 66 patients (89.4%) colonisation cultures of the throat, perineum, and respiratory tract were obtained in time, i.e. within 48 hours after start of mechanical ventilation (SWAB indicator 1). In 44 out of 66 patients (66.7%) two sets of colonisation cultures of the throat, perineum and respiratory tract per week were obtained during the entire episode of mechanical ventilation (SWAB indicator 2). The SDD dose was doubled in 10 out of 38 patients (26.3%) when the second colonisation culture of the throat, perineum, or respiratory tract grew gram-negative microorganism (SWAB indicator 3).

Physicians stopped third-generation cephalosporin therapy as part of SDD after four days in 44 out of 46 patients (95.7%) (SWAB indicator 4). For the remaining 4.3%, a valid reason was found for continuing cephalosporin therapy after four days (e.g. an ongoing infection for which targeted therapy with a third-generation cephalosporin was justified).

In 33 out of 66 patients (50%) oral SDD was given four times daily (SWAB indicator 5). In 30 out of 66 patients (45.5%) enteral SDD

was given four times daily (SWAB indicator 6). Adherence to the protocol was consistent throughout the episode of mechanical ventilation. Oral and enteral SDD was mainly forgotten at 24.00 hours, in 85.5% of all oral SDD administrations and in 84.9% of all enteral SDD administrations.

Live observations (n=30) showed that in all patients (100%) the four steps of administering oral and enteral SDD (preparation, first signature, second signature, and administration of SDD) were performed accurately, even if signatures were incomplete.

Discussion

Our study showed that in an ICU of a large teaching hospital, approximately 90% of patients received the recommended antibiotic care for obtaining surveillance cultures when SDD is applied, obtaining colonisation cultures in time, and stopping third-generation cephalosporin therapy as part of SDD after four days (NICE indicator 4, SWAB indicator 1 and 4). Approximately 70% of the patients received the recommended antibiotic care for performing blood cultures at the start of antibiotic therapy, determining blood levels in time when TDM is indicated, and obtaining two colonisation cultures per week (NICE indicator 2 and 3, SWAB indicator 2). Concerning the indicator 'doubling of SDD dose if required by protocol' (SWAB indicator 3), only 26% of the patients received the recommended antibiotic care.

Adherence to recommend antibiotic care for the administration of oral SDD paste and enteral SDD was more difficult to interpret (SWAB indicator 5 and 6). Even though the retrospective analysis of patients' medical and nursing records showed that only 50% of the patients received the recommended antibiotic care, the live observations showed full adherence scores (100%). Thus, the rate of administering SDD paste and enteral SDD is probably higher than what is registered in the paper-based nursing records. While trying to explain this by asking ICU nurses, it became clear that nurses do not see the necessity to double-check (putting down a second signature) the administration of oral and enteral SDD since they consider SDD to be 'prophylaxis', not therapy. In addition, there is no specific note of dosage on the SDD package, thus nurses cannot administer a wrong dosage to the patient.

Even if live observations showed full compliance, there is not an exact control of the amount of oral SDD paste administered to oropharyngeal mucosa of the patient. However, it is practically impossible to let another nurse check whether all the paste is applied to the mucosa. It is important to inform nurses about the benefits of administering oral SDD paste and what happens if it is done incompletely. Feedback of repeated positive throat colonisation cultures (with SDD sensitive microorganisms) in daily patient rounds could improve the effectiveness of application practice.

In a Dutch multicentre ICU study compliance to administration of SDD was reported to be 97.5%. This multicentre study found that noncompliance with the SDD medication mostly occurred at the end of the ICU stay, which was due to the patient's decision to decline the SDD paste.[23] Our study shows that adherence to recommendations in a controlled study setting does not always reflect the application in clinical practice. Especially the application of SDD at night time is vulnerable. This is important as the benefits of SDD on patient outcomes such as the prevention of development of severe infections during ICU stay and even mortality may depend heavily on adherence to these recommendations. Furthermore, the effects of SDD underdosing may influence the gut microbiome in an unfavourable way, possibly selecting antibiotic-resistant Enterobacteriaceae. Therefore, we suggest to optimise SDD application, for example by changing the night administration time from 24.00 to 22.00 hours in selected patients and standardising the amount of oral SDD paste that is administered.

The performance of blood cultures at the start of antibiotic therapy (NICE indicator 2) by physicians and nurses was 75.4% in this study, which is higher than what was measured in previous reports (adherence of 36% and 57%).[24,25] However, these previous studies were performed in a non-ICU setting.[24,25] Even though our study was performed in only one hospital, our results suggest that adherence to the recommendation to perform blood cultures at the start of antibiotic therapy is better in patients who are in the ICU than in a non-ICU setting.

In 89.4% of patients colonisation cultures were obtained on admission (SWAB indicator 1) and in 66.7% two sets of colonisation cultures were obtained every week (SWAB indicator 2). This is in line with previous studies, where adherence to obtaining colonisation cultures on admission and twice a week thereafter was 87% for perineum samples and 87% for respiratory tract samples.[23] Nevertheless, in our study most physicians and nurses failed to obtain a colonisation culture of the respiratory tract. In all mechanically ventilated patients these cultures should be easy to collect even if patients do not produce sputum spontaneously.

In order to improve compliance to performance of blood and colonisation cultures, reminders could be added to the electronic patient file. However, it is important to take into consideration the acceptability of yet another reminder in daily nursing practice.

In our study, days of therapy per 100 patient-days was 102.8 in 2016. This is higher than what was measured in a previous Dutch trial, in which days of therapy per 100 patient-days was 84.[26] However, Van Daalen et al. excluded ICU patients in whom antibiotic use is abundant,[5] which probably explains the difference in days of therapy per 100 patient-days. In addition, Van Daalen et al. only included those patients who entered the trial, so no fair comparison is possible.

Days of therapy is considered a reliable measure for benchmarking quantity of antimicrobial use with other departments or hospitals and may help to determine where to set priorities to improve antibiotic use. However, since this

study only focuses on one department in one hospital, in this setting, the indicator does not tell us much.

Strengths and limitations

The strength of our study is that we assessed an extensive set of quality indicators for antibiotic use, including SDD, in ICU patients. To our knowledge this is the first study to measure the adherence to recommendations for SDD use in ICU patients in daily practice. In addition, we used fixed algorithms specifically developed for the defined quality indicators.[27] The data to compute the quality indicators were extracted in a uniform way. This study also has some limitations. First, the SWAB quality indicators were not developed using a consensus procedure among experts but derived from the national SWAB guideline[22] and the local hospital guideline for SDD use in ICUs. Nevertheless, these guidelines were based on a consensus method with experts. Second, for the SWAB quality indicator 'doubling of SDD dose if required by protocol', only the colonisation cultures for gram-negative bacteria and not for yeasts were investigated. According to the local hospital guideline for SDD (but not the national guideline) both colonisation cultures for gram-negative bacteria and for yeasts should be obtained. This means that the percentage of adherence for 'doubling of SDD dose if required by protocol' would have been even lower if the local protocol was used when calculating adherence scores. Besides this difference, the local guideline is in line with the national guideline. Third, this study recruited participants from only one non-university teaching hospital in the Netherlands, which limits the generalisability of our results. However, we included all sequential patients admitted to the ICU who received antibiotics, which enhanced representability of the patient sample of this hospital.

Conclusion

This study shows that, overall, patients receive the recommended antibiotic care for obtaining surveillance and colonisation cultures, stopping third-generation cephalosporin therapy, performing blood cultures, and determining blood levels in time when TDM is indicated. This study also shows that there is room for improvement in doubling the dose of SDD if required by protocol. The quality indicators analysed in this study can be used by antibiotic stewardship teams to determine where to set priorities to improve antibiotic use and where to acknowledge successes in critically ill patients. Stewardship teams should discuss the quality indicators and insight should be gained into the barriers and facilitators that influence recommended use. Such information is important to develop effective interventions that improve appropriateness of antibiotic use at the ICU.

Disclosures

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