Major article

Prospective audit for antimicrobial stewardship in intensive care: Impact on resistance and clinical outcomes

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Background: The impact of antimicrobial audit and feedback on outcomes of critically ill adults is unclear. Methods: A prospective study was performed in the intensive care units (ICU) of a public hospital in Atlanta, GA. Critically ill adults receiving empiric imipenem or piperacillin-tazobactam were eligible. Outcomes for 3 periods were compared: baseline (B, February to May 2006), model 1 (M1, October 2006 to July 2008), and model 2 (M2, September 2008 to February 2009). No audit was performed during B. During M1, an infectious diseases physician evaluated patients, and a critical care pharmacist communicated recommendations to the treating team. During M2, an infectious diseases physician directly participated in interdisciplinary rounds with the medical ICU team.

Results: One hundred ninety-four patients were included during B, 415 during M1, and 83 during M2. M1 and M2 were associated with appropriate antimicrobial selection (B, 70%; M1, 78%; M2, 82%; \( P = 0.042 \)) and with lower rates of resistance (B, 31%; M1, 25%; M2, 17%; \( P = 0.033 \)). Logistic regression analysis confirmed that audit and feedback were independently associated with appropriate antimicrobial selection and prevention of resistance. The association remained strongest for M2.

Conclusion: Audit and feedback had an influence on antimicrobial prescription patterns in the ICU with a favorable impact on the emergence of resistance.

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The World Health Organization (WHO), the Infectious Diseases Society of America (IDSA), and other international public health organizations and medical societies have stated their commitments to define and promote strategies to prevent antimicrobial resistance. In this regard, 2 major strategies have been delineated by the IDSA: (1) infection prevention and control and (2) antimicrobial stewardship (AS), defined as the optimal selection of antimicrobial agents for the appropriate indication, dosage, and duration that results in the maximum benefit and minimum of adverse events and minimizes the development of antimicrobial resistance.\textsuperscript{3} This emphasis on appropriate antimicrobial utilization is supported by evidence indicating that antimicrobial use may be a key determinant of antimicrobial resistance emergence.\textsuperscript{2}

In their effort to promote AS, the IDSA and the Society for Healthcare Epidemiology of America published joined guidelines for the development of institutional programs to enhance AS in 2007.\textsuperscript{3} These guidelines recommend “prospective audit with intervention and feedback” (PAIF) as one of the most important strategies to reduce inappropriate antimicrobial use in hospitals. PAIF entails auditing antimicrobial prescriptions prospectively with interaction between the prescriber and an auditing infectious diseases (ID) physician or ID clinical pharmacist, who offers feedback to the prescriber on aspects related to appropriate antimicrobial use. Although there are controlled trials showing the advantages of PAIF, this evidence is limited to certain outcomes only and predominantly to patient populations with mild to moderate severity of illness.\textsuperscript{4,5} Additionally, there is a lack of standardization among PAIF approaches in the intensive care unit (ICU), such as timing and type of interventions, health professional intervening, and method of communication with treating physicians. Of particular unease is the scarcity of studies evaluating...
relevant clinical outcomes and safety in critically ill patients exposed to PAIF interventions. Indeed, most studies have used as main outcomes economic variables or somewhat subjective estimates of appropriate use, which may or may not be associated with relevant clinical outcomes. Although the main purpose of AS is to limit the emergence of antimicrobial resistance, most studies evaluating a variety of AS interventions have done so by using eco

logistic analysis of aggregate data, and only few have evaluated this outcome at a patient level in the ICU setting.

Therefore, further data regarding the impact of AS (and of PAIF as one of the main strategies) in the ICU are clearly needed, particularly because the density of antimicrobial use and the rates of antimicrobial resistance are highest in these settings. The objective of this study was to evaluate the impact of 2 AS PAIF models on relevant outcomes (mortality, emergence of resistance, appropriate antimicrobial selection, and length of stay) in critically ill patients prescribed broad-spectrum antibiotics.

METHODS

Setting

Grady Memorial Hospital is a 1,000-bed, community teaching hospital in Atlanta, GA. An antimicrobial stewardship program was established at Grady Memorial Hospital in 2001. Since then, both an ID physician and an ID clinical pharmacist have been core members of the program. PAIF for the ICUs is performed by the ID physician with the support of the critical care (non-ID) pharmacists. In general, audit is triggered by the prescription of targeted antimicrobials, which is followed by case evaluation and, if necessary, communications with the treating physicians. The ICUs at Grady Memorial Hospital are “closed,” meaning that the care of these patients is under the responsibility of interdisciplinary teams led by physicians with specialty training in critical care medicine. Because of the academic affiliation of Grady Memorial Hospital, the interdisciplinary teams include several physicians at different levels of training (interns, residents, and fellows); in addition, other health care workers are part of the team, including nurses, respiratory therapists, and critical care pharmacists. The study was approved by the Emory University Institutional Review Board and the Grady Memorial Hospital Research Oversight Committee.

Design and definitions

This was a prospective quasi-experimental study. Adult patients cared for by the medical ICU (MICU) or the surgical ICU (SICU) teams and who were receiving empirically any of the targeted broad-spectrum antibiotics (≤3 days of antibiotic treatment duration and antibiotic started without knowledge of the causative pathogen) were considered eligible for inclusion. The targeted antibiotics were imipenem and piperacillin-tazobactam. Patients were excluded if they were concurrently evaluated by the ID consultation service. The main outcome variables were hospital mortality, emergence of resistance, appropriateness of antimicrobial selection, and length of stay after antibiotic initiation.

Appropriate antimicrobial selection was defined as target antimicrobial selection in accordance with local hospital guidelines for empiric antimicrobial use. Details about the criteria for appropriate antimicrobial selection for the targeted antimicrobials are available at the Grady Memorial Hospital Antimicrobial Utilization Web site (http://www.gradyantibiotics.com/; tabs “Antimicrobial Restrictions and Criteria for Category II Antimicrobials”).

For each patient included in the study, emergence of resistance was considered present when any clinical culture performed between 3 and 28 days after antibiotic initiation revealed at least 1 of 13 predefined microorganisms of clinical or epidemiologic interest (Table 1) and the same organism was not recovered from any clinical culture within 28 days before and 2 days after antibiotic initiation.

Interventions and control

During the baseline (control) period (February to May 2006), no AS PAIF activities were performed, and data were collected on both MICU and SICU patients. During the “Model 1” (M1) period (October 2006 to July 2008), PAIF consisted of unlimited patient evaluation by an antimicrobial utilization physician, a board certified ID specialist, the director of antimicrobial utilization at the hospital, and communication of recommendations to the primary ICU team, using a written document discussed with the critical care pharmacist. The written document was not incorporated into the patient’s medical history. In addition, the critical care pharmacist participated consistently in interdisciplin ary rounds with the ICU team. The antimicrobial utilization physician evaluated patients cared for by the SICU or MICU teams following a monthly sequence (1 month dedicated to 1 type of ICU, the following month dedicated to the other type of ICU). Patients were followed by the antimicrobial utilization physician for 5 to 7 days or until ICU discharge (whichever occurred first). For months during which the antimicrobial utilization physician was not evaluating patients cared for by one of the ICU teams, PAIF for those patients was performed solely by the critical care pharmacists.

During the “Model 2” (M2) period (September 2008 to February 2009), the same antimicrobial utilization physician participated in interdisciplinary rounds with the ICU team 3 times per week, with a critical care pharmacist continuing daily participation. The intervention during M2 was restricted to patients cared for by the MICU team. During both M1 and M2 periods, the feedback provided to the critical care teams was related to any aspects of infection management and antimicrobial use, with recommendations not restricted to the utilization of the targeted antimicrobials.

Statistical analysis

Numeric variables were described as mean and standard deviation and categorical variables as counts and frequencies. Univariate analysis was performed using Student t test for numeric variables and χ² or Fisher exact test for categorical variables. Multivariate analysis was performed using logistic regression (Wald test) to explore independent predictors of emergence of resistance, mortality, and appropriateness of antimicrobial selection adjusting for baseline variables and possible confounders. Exploratory analyses restricted to MICU patients were also performed to assess possible confounding by ICU type. P values less than .05 were considered significant. Statistical analyses were carried out using SAS software version 9.1 (SAS Institute, Cary, NC).

RESULTS

A total of 692 patients was prospectively included in the study: 194 during the baseline period, 415 during M1, and 83 during M2. During M1, 196 patients (47%) were evaluated by the antimicrobial utilization physician. Although imipenem and piperacillin-tazobactam were the antibiotics targeted for determining patient eligibility, 90% of included patients were concurrently exposed to other antimicrobial classes (75%, 26%, and 23% were coexposed to vancomycin, amikacin, and fluoroquinolones, respectively). A prospective evaluation of the first 648 recommendations given during the M1 period indicated that, overall, 66.5% of ICU team decisions were in agreement with the antimicrobial utilization
physician recommendations (58% for SICU patients and 80% for MICU patients).

Baseline variables are presented in Table 2. MICU patients accounted for 52% of patients overall, and for 51%, 43%, and 100% of patients included during the baseline, M1 and M2 periods respectively. Patients included during the baseline and M1 periods were significantly more likely to be male and to have recent trauma and an unknown source of infection. Patients included during M2 period were significantly more likely to be 50 years of age or older and to have comorbid conditions, pneumonia as the presumptive source of infection, and a higher severity of illness at the time of antibiotic initiation.

Exploratory bivariate analysis was performed assessing variables associated with the main outcomes. Although not statistically significant, hospital mortality for patients included during M2 period (32%) was slightly higher than for those included during the other 2 periods (26% during baseline, 25% during M1). This difference was not apparent once the analysis was restricted to MICU patients (mortality of 35%, 30%, and 32% for patients included during baseline, M1, and M2, respectively, overall, \( P = .68 \)). Hospital stay, ICU stay, and antibiotic therapy duration were shortest for patients included during M2, and the difference was significant for all 3 variables for the comparisons of M2 versus M1, and for the variables hospital stay and ICU stay for the comparisons of M2 versus baseline. However, these differences disappeared once the analysis was restricted to MICU patients only (data not shown). The frequencies of resistance emergence were significantly lower (25% and 17%, respectively), and appropriate antimicrobial selection rates were significantly higher (78% and 82%, respectively) during M1 and M2 compared with baseline (resistance emergence 31%, appropriate selection 70%), with similar (although nonsignificant) trends observed when the analysis was restricted to MICU patients (emergence of resistance 25%, 18%, 17% and appropriate antimicrobial selection 71%, 76%, 82% for baseline, M1, and M2, respectively). During the M1 period, the main outcomes were not different between patients evaluated and not evaluated by the antimicrobial utilization physician (data not shown).

Multivariate logistic regression analysis was performed to assess independent determinants of mortality. There was no association between M1 and M2 with mortality. APACHE 2 score at the time of antibiotic initiation was the main determinant of mortality \( (P < .01) \), with presence of comorbidities showing a trend toward an association \( (P = .06) \).

Independent predictors of the emergence of antimicrobial resistance are presented in Table 3. According to this model, M1 and M2 were independently associated with protection against the emergence of resistance, with M2 showing the strongest association. In a separate analysis combining the 2 PAIF models as “any model” (data not shown), the overall odds ratio for the association with resistance was estimated to be 0.4 (95% confidence interval: 0.25-0.62; \( P < .01 \)). Surgical ICU patients and the number of cultures performed after antibiotic initiation were also independently associated with the emergence of resistance as defined in the study.

Table 4 shows independent predictors of appropriate antimicrobial selection. Both M1 and M2 showed trends toward and independent association in this model, with a stronger association observed for M2. In a similar model combining both M1 and M2 as “any model,” a significant and independent association with appropriate antimicrobial selection was observed (odds ratio, 1.5; 95% confidence interval: 1.02-2.24; \( P = .04 \)).

**DISCUSSION**

Both M1 and M2 are in line with the recommendations by the Society of Critical Care Medicine Outcomes Task Force guidelines on how to implement, evaluate, and maintain an interdisciplinary quality improvement program in the intensive care unit. According to these guidelines, leadership, motivation, and teamwork are the foundation for a successful quality improvement intervention, which should introduce strategies likely to change behavior. Behavioral change in physicians is difficult to accomplish, and audit and feedback of recent performance are the backbone of successful quality improvement initiatives. Informal discussions and formal presentations by local leaders to the involved team as well as frequent reminders and interactive educational interventions are useful for inducing and sustaining change.

Favorable outcomes were observed for both models. The observation that outcomes were not different between patients evaluated and not evaluated by the antimicrobial utilization physician during the M1 period was unexpected, given that
there was consistent feedback to the critical care teams provided by the critical care pharmacists, who serve as ambassadors of the antimicrobial utilization physician messages and acted as multipliers of antimicrobial management knowledge and local policies.

The results of this study suggest that M2 may be associated with a larger effect on the assessed outcomes compared with M1. These may be explained by the following differences between models: (1) During M2, real-time feedback came directly from a local antimicrobial utilization leader, rather than from the critical care pharmacist; (2) the sole presence of the ID physician may have had an impact on behavior, and it also may have facilitated interactive educational interventions as well as real-time discussion of challenging recommendations, which otherwise could have been received with discomfort by the critical care physicians.

It is always important to assess the impact of any tested AS strategy on relevant clinical outcomes because a given intervention can only be justified if favorable appropriateness-of-use or resistance-related outcomes are seen with neutral or favorable clinical impact. This is particularly relevant for critically ill patients, whose outcomes have been associated with the timely administration of active antimicrobial agents against the offending microorganism. In fact, there is potential risk, perceived mostly by critical care physicians, that the emphasis placed by AS on controlling antibiotic use could lead to increases in patient risk. This is partially supported by some studies suggesting that certain AS activities may be associated with undesired clinical outcomes. To date, no other study to the author’s knowledge has evaluated the safety of AS PAIF in the ICU. The models evaluated resulted in at least neutral effects on mortality and hospital stay and therefore seem beneficial overall.

The presented models have implications that may influence the decision of whether or not similar interventions should be instituted in a particular ICU. Although the models were well received by the ICU teams and allowed the final decisions to be taken by the critical care physicians, M2 in particular was perceived by some as an interference with the flow of ICU rounds that demanded extra time and dedication and others felt some degree of threat to their autonomy. Additionally, the amount of time spent by the ID physician on both models was considerable, requiring approximately 0.3 to 0.5 full-time equivalents of ID physician time. The economic implications of this are likely offset by the benefits derived from the models, but this may be seen as an implementation barrier from the perspective of hospital administrators.

This study has several limitations. It is a single center study, which may condition the external validity of the results to acute care hospitals similar to Grady Memorial Hospital with regards to size, academic affiliation, AS resources, and ICU care structure. The study definition of emergence of resistance at a patient level is not standardized, but it was defined a priori and is easily adaptable to other institutions. The main limitation of the study lies in the quasi-experimental design because it is possible that seasonal variations or nonquantified, time-dependent variables may have confounded study estimates; although infection control interventions were largely unchanged during the study periods, other events may have influenced antimicrobial prescription patterns or resistance rates.

In conclusion, this study suggests that AS PAIF can be safely performed and that it may have a favorable impact on antibiotic use patterns and the emergence of antimicrobial resistance in the ICU setting. Confirmation of these findings would require larger and multicenter studies.

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References