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Crit Care Med. Author manuscript; available in PMC 2014 November 01.

Published in final edited form as:
Crit Care Med. 2013 November ; 41(11): . doi:10.1097/CCM.0b013e318298291a.

A clinical trial comparing physician prompting with an unprompted automated electronic checklist to reduce empirical antibiotic utilization

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Abstract

Objective—To determine whether face-to-face prompting of critical care physicians reduces empirical antibiotic utilization compared to an unprompted electronic checklist embedded within the electronic health record (EHR).

Design—Random allocation design.

Setting—Medical intensive care unit (MICU) with high-intensity intensivist coverage at a tertiary care urban medical center.

Patients—Two hundred ninety-six critically ill patients treated with at least one day of empirical antibiotics.

Interventions—For one MICU team, face-to-face prompting of critical care physicians if they did not address empirical antibiotic utilization during a patient's daily rounds. On a separate MICU team, attendings and fellows were trained once to complete an EHR-embedded checklist daily for each patient, including a question asking whether listed empirical antibiotics could be discontinued.

Measurements and main results—Prompting led to a more than 4-fold increase in discontinuing or narrowing of empirical antibiotics compared to use of the electronic checklist. Prompted group patients had a lower proportion of patient-days on which empirical antibiotics were administered compared to electronic checklist group patients (63.1% vs. 70.0%, P=0.002). Mean proportion of antibiotic-days on which empirical antibiotics were used was also lower in the prompted group, although not statistically significant (0.78 [0.27] vs. 0.83 [0.27], P=0.093). Each additional day of empirical antibiotics predicted higher risk-adjusted mortality (odds ratio 1.14, 95% CI 1.05–1.23). Risk-adjusted ICU length of stay and hospital mortality were not significantly different between the two groups.

Conclusions—Face-to-face prompting was superior to an unprompted EHR-based checklist at reducing empirical antibiotic utilization. Sustained culture change may have contributed to the electronic checklist having similar empirical antibiotic utilization to a prompted group in the same

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The rest of the authors have not disclosed any potential conflicts of interest.

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MICU two years prior. Future studies should investigate the integration of an automated prompting mechanism with a more generalizable EHR-based checklist.

Keywords

prompting; physician decision-making; checklists; empirical antimicrobial agents; process of care

INTRODUCTION

Checklists reduce errors of omission and improve outcomes in critically ill patients.[1–7] The most effective use of checklists includes a forcing function, such as empowering nurses to stop a procedure.[2–4] Compared to the unprompted use of a written checklist, face-to-face prompting of critical care physicians improves multiple process of care (POC) parameters, including reducing the utilization of empirical antibiotics.[8, 9] Prompting is also associated with lower risk-adjusted mortality and length of stay.[8]

Face-to-face prompting by a physician who is not normally a part of the multidisciplinary team is not easily scalable to clinical practice. Furthermore, paper checklists may become cumbersome and their effectiveness curtailed by poor standardization. Others have demonstrated the potential utility of telemedicine, non-real-time printed reminders, or electronic decision support tools.[7, 10–12]

Empirical antibiotic utilization has clinical significance and can be a target of POC improvement. Patients frequently receive empirical antibiotics despite low likelihood of infection.[13] Prolonged empirical antibiotic duration can lead to superinfection or antibiotic resistance and can predict risk-adjusted mortality, whereas strategies that reduce empirical antibiotics are associated with either no change or lower risk-adjusted mortality.[9, 14–18] Shortened duration of empirical antibiotics may account for some of the mortality benefits previously seen with prompting.[8, 9]

We sought to compare real-time, face-to-face prompting with an unprompted checklist embedded within the electronic health record (EHR) for reducing the utilization of empirical antibiotics. We hypothesized that prompting would be superior to an unprompted electronic checklist in reducing the proportion of empirical antibiotics administered to patients and empirical antibiotic duration. In addition, lower mortality in association with greater changes in empirical antibiotics would add further support to the role excessive empirical antibiotics may play in intensive care unit (ICU) mortality.

METHODS

Setting

The study was conducted in the medical ICU (MICU) at Northwestern Memorial Hospital (NMH), a tertiary care urban university-affiliated hospital. The MICU is a closed unit with high-intensity intensivist coverage by two teams, each with an independent patient census. Teams admit patients on alternating days, and patients are rarely redistributed between the teams. Each team consists of one pulmonary/critical care attending physician, one fellow, one pharmacist, and several residents and interns. Attendings have weekday rotations of 1–2 weeks while fellows have weekday rotations of 1–6 weeks. Weekend coverage is frequently different for attendings and fellows.

Study Design

We conducted a random allocation design trial comparing an EHR-based checklist to a face-to-face physician prompter. The MICU teams were randomized to the interventions by coin

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flip. The study was approved by the Institutional Review Board and was registered with Clinicaltrials.gov (NCT01396044). All patients admitted to the MICU on or after June 27, 2011, discharged on or prior to October 7, 2011, and who received at least one day of empirical antibiotics were included. This time period was chosen to minimize crossover of attendings and fellows between the two teams, which would have contaminated the independence of the teams. Exclusion criteria included patients transferred to or from a different ICU service and any MICU re-admissions without an intervening hospital discharge (first MICU admissions were included).[19, 20]

Intervention

Physician prompting—We have previously described the face-to-face prompting methods employed in this study.[8] In brief, a non-care providing resident physician joined daily bedside rounds of one of the MICU teams. If a patient was being treated with an antimicrobial agent and the team had not addressed this topic during the course of rounds, the prompter initiated discussion with the team using scripted questions. These questions were: 1) “Why is the patient on [antibiotic]?” and 2) “The [test (e.g. blood culture)] was [negative/positive] for [X (e.g. bacteria)]. Do you plan to continue [antibiotic]?” This team had a simplified paper checklist which included six other parameters in addition to empirical antibiotics. The electronic checklist was available to this team, although they were not specifically shown how to access it. Prompters had no patient care responsibilities, and there was no contact between prompters and patients. Prompting was directed at the attending and fellow, and occurred after a care-providing resident’s presentation but before the MICU team entered the patient’s room. Prompting continued for each patient on a daily basis (whenever the prompter was present) until MICU discharge.

Electronic Checklist—The other MICU team used a checklist embedded within the EHR. This checklist was developed to provide a centralized source of information on antibiotic utilization in addition to six other parameters (Supplemental Figure 1). Actively used antibiotics are automatically listed, including name, dose, and schedule. A question asks “Can antibiotic coverage be stopped or narrowed today?” with radio buttons for a provider to indicate a response. Attendings and fellows randomized to the electronic checklist arm were instructed at the beginning of their rotation on the location of the checklist within the EHR and how to complete it; they were encouraged to use the checklist daily for each patient. After this initial instruction, no further encouragement was given. Completion of the electronic checklist required providers to 1) remember to use the checklist, 2) access the checklist in the EHR, 3) review the antibiotic section, and 4) electronically sign. No daily electronic prompt to complete the checklist was generated and no forcing function to complete the electronic checklist was used. The checklist was accessible by searching for “ICU checklist” in an order box within the EHR. The simplified paper checklist was also available to this team.

Outcome assessment

The *a priori* primary outcomes were differences between electronic checklist and prompted group patients in empirical antibiotic duration and the proportion of antibiotic-days on which empirical antibiotics were used during ICU stay. Empirical antibiotics were defined as any antimicrobial agent administered without culture-documented infection.[8] Secondary outcomes included: physician-reported indication for antibiotics (definitions were based on the 2005 International Sepsis Forum consensus statement and the 2008 Society of Critical Care Medicine’s guideline for evaluating fever in the critically ill) (Supplemental Table 1); distribution of antibiotics used; microbial culture and other pertinent diagnostic test results; ICU and hospital mortality; ICU and hospital length of stay; and Acute Physiology and Chronic Health Evaluation (APACHE) IV predicted mortality and length of stay.[19–22]

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We also measured the frequency of prompting in the prompted group and how often prompting led to a change in management, and the electronic checklist completion rate. Data were obtained by direct observation by research personnel or from the EHR or Northwestern Enterprise Data Warehouse (EDW).

Statistical Analysis

Descriptive data are summarized as mean (standard deviation, SD), median [interquartile range, IQR], or number (%). We used a χ^2 test to compare categorical variables, and Student's t test or Wilcoxon rank-sum tests to compare continuous variables, as appropriate.

The prior study results for the mean (SD) proportion of antibiotic-days on which empiric antibiotics were used were as follows: prompted 0.77 (0.32), control 0.91 (0.29).[8] Assuming a two-sided α=0.05 and power 1−β=0.80 and equal sample sizes, a sample size of 75 patients per group would be required to detect this difference. While our study duration was limited to minimize crossover of physicians between the types of prompting, the number of admissions during the anticipated study period provided adequate power to demonstrate this difference.

We constructed a logistic regression model to adjust hospital mortality for APACHE IV predicted hospital mortality and ICU admission diagnosis. We constructed a separate logistic regression model to assess whether empirical antibiotic duration is associated with risk-adjusted hospital mortality. Differences are expressed as the odds ratio (OR) for death with 95% confidence intervals (CIs). We calculated standardized mortality ratios (SMR, observed/APACHE IV predicted mortality) reported with 95% CIs. Regression analysis was used to adjust ICU length of stay for APACHE IV predicted length of stay (LOS). All tests are two-tailed, and a *P* value of <0.05 was considered significant. Analyses were performed using Stata (version 11, College Station, TX).

RESULTS

Two hundred ninety-six patients were included (Figure 1). Baseline characteristics are shown in Table 1.

Empirical antibiotic outcomes

Empirical antibiotics were administered on a lower proportion of patient-days in the prompted compared to electronic checklist group (63.1% vs. 70.0%, *P*=0.002). A trend toward a lower mean (SD) proportion of antibiotic-days on which empirical antibiotics were administered was also found in the prompted group (0.78 [0.27] vs. 0.83 [0.27], *P*=0.093) (Table 2).

Empirical antibiotic duration was associated with an increase in risk-adjusted hospital mortality (OR per additional empirical antibiotic day 1.14, 95% CI 1.05–1.23, *P*=0.002). Using empirical antibiotic duration of 1–3 days as a reference, empirical antibiotic duration ≥ 7 days was associated with increased risk-adjusted hospital mortality (OR 3.2, 95% CI 1.5–6.8, *P*=0.002). Empirical antibiotic duration of 4–6 days was not associated with a change in risk-adjusted mortality (OR 1.3, 95% CI 0.55–3.1, *P*=0.55).

We performed sub-analyses of empirical antibiotic outcomes stratified by the likelihood of infection. A significantly lower proportion of patient-days on which empirical antibiotics were administered occurred in the prompted group compared to control for patients with possible infection/empirical indication (65.7% vs. 73.0%, *P*=0.002) (Table 3). No differences in empirical antibiotic utilization were found in patients classified as having definite or probable infection.

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In the electronic checklist arm, thirty-five patients did not have electronic checklist completion data in the EDW; all of these patients had an ICU LOS less than 24 hours. An electronic checklist was completed on 166 patient-days; when the electronic checklist was completed, 16 (9.6%) patient-days were associated with narrowing or discontinuing empirical antibiotics.

In the prompted arm, a prompter was present on 72% of study days. Fifty-five patient-days required prompting to address empirical antibiotic utilization. When prompting occurred, 24 (43.6%) patient-days were associated with subsequent narrowing or discontinuing of empirical antibiotics (comparison with electronic checklist rate, P<0.001). Vancomycin was the most common antibiotic requiring prompting.

Clinical outcomes

As shown in Table 4, no difference in median [IQR] ICU LOS was found between prompted and electronic checklist groups (2.6 [1.5–6.9] days vs. 2.8 [1.7–6.5] days, P=0.27). In regression analysis, group assignment did not predict risk-adjusted ICU LOS (P=0.90).

No significant difference in unadjusted hospital mortality between the prompted and control groups was found (17.5% vs. 24.0%, P=0.17). The electronic checklist group had higher APACHE IV predicted mortality compared to the prompted group (34.2% vs. 27.5%, P=0.043). However, the SMR (95% CI) for both the prompted (0.64 [0.43–0.92]) and electronic checklist (0.70 [0.47–1.0) groups were both significantly lower than 1.0 (P<0.05 for both comparisons) but not different between the two groups (Table 4).

DISCUSSION

In this study, prompting physicians was superior to unprompted use of an electronic checklist in reducing empirical antibiotic administration to critically ill patients. This outcome was observed for both the proportion of patient-days on which empirical antibiotics were administered and the proportion of all antibiotics that were administered empirically.

These results support the importance of real-time prompting to achieve beneficial change in critical care physician decision-making, building on prior pre/post research that demonstrated a similar impact of real-time reminders.[23, 24] The electronic checklist did not incorporate real-time reminders or alerts, nor did it necessarily elicit peer-to-peer discussion. Consequently, even when conscientious physicians completed the electronic checklist, a change in management (checking “Yes” to a question about whether antibiotics could be discontinued or narrowed) only occurred on 9.6% of patient-days. In contrast, face-to-face, real-time prompting led to a change in management on 43.6% of patient-days.

We believe this striking discrepancy speaks to mechanisms critical for physicians to change their decision-making behavior, particularly for more nuanced decisions such as antibiotic treatment of critically ill patients or readiness to wean from mechanical ventilation. An electronic checklist can effectively integrate data and may be very effective for more discrete or single point-in-time decisions, such as need for stress ulcer prophylaxis or type of deep venous thrombosis prophylaxis. An electronic checklist is clearly a more scalable intervention than the physical presence of a physician whose sole purpose is to prompt other physicians on rounds. While others have shown that standardization and checklists may improve care, our study suggests that an intervention without mechanisms to prompt both completion and response to checklist items compromises the potential for real POC or clinical benefits.

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We chose to investigate the burden of empirical antibiotics based on our prior experience with this POC measure and its known impact on clinical outcomes.[8, 9] Others report similar adverse effects of excessive empirical antibiotics in the ICU.[14–17, 25–32] Our study supports these prior findings by demonstrating that each one day increase in empirical antibiotic duration is associated with a 14% relative increase in risk-adjusted mortality, and that fewer empirical antibiotics are not associated with worse clinical outcome.

We also focused on empirical antibiotics because antibiotic management in the critically ill is a complex decision matrix, with a great degree of diagnostic uncertainty. In addition, the decision to continue or change empirical antibiotics is made daily with the default decision generally to continue. We correspondingly found a greater effect of prompting in patients who did not have probable or definite infection. Other strategies can counteract this tendency to continue empirical antibiotics, such as automatic stop orders and pharmacist-driven protocols, but may put the patient at risk for missed therapy and induce conflict between medical services based on competing priorities.[33, 34] One advantage of face-to-face prompting may be more extensive conversation between multiple services.

Comparing this study with our previous study, which compared face-to-face prompting to a paper checklist for six POC parameters in the same MICU two years prior to the current study, reveals important observations.[8] The mean proportion of empirical antibiotics administered to patients in the electronic checklist group in this study was identical to that of patients whose physicians were prompted in our prior study, and significantly lower than the prior study's paper checklist control group. The percentage of patient-days on which empirical antibiotics were administered was similar in the electronic checklist group in this study and the prompted group in the prior study (70.0% vs. 72.1%).

These similarities may be due to a retained culture change regarding the adverse effects of excessive empirical antibiotics that was adopted by our physicians and persisted for the two years between studies. Results of the original study, particularly concerning empirical antibiotics, were widely discussed among our physicians, nurses, pharmacists, and other staff. Sustained culture change is consistent with the findings in the electronic checklist arm of this study, with both decreased empirical antibiotic use and corresponding lower SMR than the prior control group. In addition, the equivalent empirical antibiotic use in the prior study prompted group and the current study electronic checklist group suggests that the prior results were unlikely to be due to a Hawthorne effect from having research personnel on rounds.

However, lower baseline empirical antibiotic use and SMR are the most likely explanation for a lack of significant differences between study arms in associated mortality or LOS as compared to our previous study. Multiple other factors affect mortality and LOS in the critically ill, and we may have achieved the maximal mortality and LOS benefits of decreased empirical antibiotic use with the degree of changes induced by the prior study. It is possible that reducing empirical antibiotic utilization has an impact on other outcomes, such as lowering the risk of future antibiotic resistance or cost.

There are several potential limitations. As a single-center study, the generalizability of the results may be limited in other ICUs and non-ICU settings. Second, the study population was relatively small; we limited the length of the study to minimize crossover of physicians between the two teams. While some crossover did occur (two weekday and three weekend attendings out of 19 total attendings; one weekday fellow out of 10 total fellows), we believe this was minimal and any crossover would likely bias the results toward the null, leading to underestimation of the magnitude of treatment effect. Relatedly, a cross-over study design was not entertained due to concern about the length necessary for a wash-out period. Third,

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randomization was performed at the level of the ICU team. Since the intervention was targeted to attendings or fellows, lack of clustering by physician could have influenced results. However, as described previously, patients are cared for by multiple attending physicians during their ICU stay since physicians rotate “on-service” frequently.[9] No established method exists to account for clustering when multiple providers per patient are involved. This likely diminishes the influence of any individual physician, making the lack of clustering less significant. Fourth, this study was not powered to detect differences in length of stay or mortality. Finally, team characteristics or individual practice patterns could differ by team, leading to confounding. However, this concern is mitigated in part by multiple physicians caring for many patients described above.

Future studies should seek to merge the advantages of automated information delivery with a mechanism of prompting physicians to use that information. We believe a face-to-face, multidisciplinary discussion of complex POC issues is optimal. However, the prompting mechanism we have developed, which relies upon resident physicians independent of the care-providing multidisciplinary ICU team, is impractical outside the research setting. Successful implementation interventions with tele-ICU alerts from a command center physician or another form of external support are equivalent strategies but are also expensive and require availability of more senior level physicians.[7, 10] Whether designating other existing members of the team—midlevel providers, nurses, or pharmacists—as prompters is as effective as physician-to-physician prompting is unknown and would add new responsibilities to these providers. An electronic prompting system embedded within the EHR could combine real-time reminders with the advanced data collection and integration capabilities of the modern EHR. However, real-time electronic prompting would remove the personal aspects of direct prompting and could promote alarm fatigue. Comparative effectiveness of these approaches deserves investigation in future studies.

CONCLUSIONS

Previously we showed that prompting reduced the proportion of empirical antibiotics administered to critically ill patients compared to the unprompted use of a paper checklist; in this study, prompting was superior to an unprompted checklist embedded in the EHR. Compliance with the electronic checklist was low. Furthermore, prompting was associated with a more than 4-fold increase in the rate of decision-making behavior change. No improvements in LOS or mortality were demonstrated, but the study was underpowered for these outcomes. Real-time prompting is a POC intervention that has significant benefits for the care of critically ill patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank the faculty and fellows of the Division of Pulmonary and Critical Care Medicine, the residents of the Departments of Internal Medicine and Emergency Medicine, and the pharmacy and nursing staffs of the Medical Intensive Care Unit for including us on daily MICU rounds. We thank Dr. Alfred Rademaker, PhD (Department of Preventive Medicine and Biostatistics Collaboration Center) for his statistical review of our data and manuscript. None of these people received compensation beyond their normal salaries.

Sources of Support: National Heart Lung and Blood Institute (T32HL076139-07) and Parker B. Francis Fellowship to CHW

Dr. Weiss has received funding from the National Institutes of Health. Drs. Sung and Rho received a travel award to present a research abstract at American Thoracic Society conference in May 2012 from Northwestern University

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Feinberg School of Medicine Department of Medicine. Dr. Wunderink is a board member for Pfizer and has consulted for Crucell (now J&J), Trius, Astra Zeneca, and Glaxo Smith Klein. He has received grant support from bioMerieux and received payment for lectures from American Thoracic Society.

References

1. Berenholtz SM, Pronovost PJ, Lipsett PA, et al. Eliminating catheter-related bloodstream infections in the intensive care unit. Crit Care Med. 2004; 32:2014–2020. [PubMed: 15483409]
2. Pronovost P, Needham D, Berenholtz S, et al. An intervention to decrease catheter-related bloodstream infections in the ICU. N Engl J Med. 2006; 355:2725–2732. [PubMed: 17192537]
3. Byrnes MC, Schuerer DJ, Schallom ME, et al. Implementation of a mandatory checklist of protocols and objectives improves compliance with a wide range of evidence-based intensive care unit practices. Crit Care Med. 2009; 37:2775–2781. [PubMed: 19581803]
4. Haynes AB, Weiser TG, Berry WR, et al. A surgical safety checklist to reduce morbidity and mortality in a global population. N Engl J Med. 2009; 360:491–499. [PubMed: 19144931]
5. Dubose J, Teixeira PG, Inaba K, et al. Measurable outcomes of quality improvement using a daily quality rounds checklist: one-year analysis in a trauma intensive care unit with sustained ventilator-associated pneumonia reduction. J Trauma. 2010; 69:855–860. [PubMed: 20032792]
6. DuBose JJ, Inaba K, Shiflett A, et al. Measurable outcomes of quality improvement in the trauma intensive care unit: the impact of a daily quality rounding checklist. J Trauma. 2008; 64:22–27. discussion 27–29. [PubMed: 18188094]
7. Lilly CM, Cody S, Zhao H, et al. Hospital mortality, length of stay, and preventable complications among critically ill patients before and after tele-ICU reengineering of critical care processes. JAMA. 2011; 305:2175–2183. [PubMed: 21576622]
8. Weiss CH, Moazed F, McEvoy CA, et al. Prompting physicians to address a daily checklist and process of care and clinical outcomes: a single-site study. Am J Respir Crit Care Med. 2011; 184:680–686. [PubMed: 21616996]
9. Weiss CH, Persell SD, Wunderink RG, et al. Empiric antibiotic, mechanical ventilation, and central venous catheter duration as potential factors mediating the effect of a checklist prompting intervention on mortality: an exploratory analysis. BMC Health Serv Res. 2012; 12:198. [PubMed: 22794349]
10. Scales DC, Dainty K, Hales B, et al. A multifaceted intervention for quality improvement in a network of intensive care units: a cluster randomized trial. JAMA. 2011; 305:363–372. [PubMed: 21248161]
11. Steurbaut K, Colpaert K, Gadeyne B, et al. COSARA: Integrated service platform for infection surveillance and antibiotic management in the ICU. Journal of medical systems. 2012
12. Steurbaut K, Van Hoecke S, Colpaert K, et al. Use of web services for computerized medical decision support, including infection control and antibiotic management, in the intensive care unit. Journal of telemedicine and telecare. 2010; 16:25–29. [PubMed: 20086264]
13. Niederman MS, Soulountsi V. De-escalation therapy: is it valuable for the management of ventilator-associated pneumonia? Clin Chest Med. 2011; 32:517–534. [PubMed: 21867820]
14. Hochreiter M, Kohler T, Schweiger AM, et al. Procalcitonin to guide duration of antibiotic therapy in intensive care patients: a randomized prospective controlled trial. Crit Care. 2009; 13:R83. [PubMed: 19493352]
15. Stolz D, Smyrnios N, Eggimann P, et al. Procalcitonin for reduced antibiotic exposure in ventilator-associated pneumonia: a randomised study. Eur Respir J. 2009; 34:1364–1375. [PubMed: 19797133]
16. Aarts MA, Brun-Buisson C, Cook DJ, et al. Antibiotic management of suspected nosocomial ICU-acquired infection: does prolonged empiric therapy improve outcome? Intensive Care Med. 2007; 33:1369–1378. [PubMed: 17558493]
17. Singh N, Rogers P, Atwood CW, et al. Short-course empiric antibiotic therapy for patients with pulmonary infiltrates in the intensive care unit. A proposed solution for indiscriminate antibiotic prescription. Am J Respir Crit Care Med. 2000; 162:505–511. [PubMed: 10934078]

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18. Kopterides P, Siempos, Tsangaris I, et al. Procalcitonin-guided algorithms of antibiotic therapy in the intensive care unit: a systematic review and meta-analysis of randomized controlled trials. Crit Care Med. 2010; 38:2229–2241. [PubMed: 20729729]
19. Zimmerman JE, Kramer AA, McNair DS, et al. Acute Physiology and Chronic Health Evaluation (APACHE) IV: hospital mortality assessment for today's critically ill patients. Crit Care Med. 2006; 34:1297–1310. [PubMed: 16540951]
20. Zimmerman JE, Kramer AA, McNair DS, et al. Intensive care unit length of stay: Benchmarking based on Acute Physiology and Chronic Health Evaluation (APACHE) IV. Crit Care Med. 2006; 34:2517–2529. [PubMed: 16932234]
21. Calandra T, Cohen J. The international sepsis forum consensus conference on definitions of infection in the intensive care unit. Crit Care Med. 2005; 33:1538–1548. [PubMed: 16003060]
22. O'Grady NP, Barie PS, Bartlett JG, et al. Guidelines for evaluation of new fever in critically ill adult patients: 2008 update from the American College of Critical Care Medicine and the Infectious Diseases Society of America. Crit Care Med. 2008; 36:1330–1349. [PubMed: 18379262]
23. Marshall J, Finn CA, Theodore AC. Impact of a clinical pharmacist-enforced intensive care unit sedation protocol on duration of mechanical ventilation and hospital stay. Crit Care Med. 2008; 36:427–433. [PubMed: 18091554]
24. Devlin JW, Holbrook AM, Fuller HD. The effect of ICU sedation guidelines and pharmacist interventions on clinical outcomes and drug cost. The Annals of pharmacotherapy. 1997; 31:689–695. [PubMed: 9184706]
25. Micek S, Johnson MT, Reichley R, et al. An institutional perspective on the impact of recent antibiotic exposure on length of stay and hospital costs for patients with gram-negative sepsis. BMC infectious diseases. 2012; 12:56. [PubMed: 22414209]
26. Johnson MT, Reichley R, Hoppe-Bauer J, et al. Impact of previous antibiotic therapy on outcome of Gram-negative severe sepsis. Crit Care Med. 2011; 39:1859–1865. [PubMed: 21499086]
27. Neuhauser MM, Weinstein RA, Rydman R, et al. Antibiotic resistance among gram-negative bacilli in US intensive care units: implications for fluoroquinolone use. JAMA. 2003; 289:885–888. [PubMed: 12588273]
28. Jacobson KL, Cohen SH, Inciardi JF, et al. The relationship between antecedent antibiotic use and resistance to extended-spectrum cephalosporins in group I beta-lactamase-producing organisms. Clin Infect Dis. 1995; 21:1107–1113. [PubMed: 8589129]
29. Levin PD, Fowler RA, Guest C, et al. Risk factors associated with resistance to ciprofloxacin in clinical bacterial isolates from intensive care unit patients. Infect Control Hosp Epidemiol. 2007; 28:331–336. [PubMed: 17326025]
30. Gentry C, Flournoy DJ, Reinert R. Analysis of antimicrobial resistance among gram-negative bacilli and antimicrobial use in intensive care unit patients for 5 years in a Veterans Affairs medical center. American journal of infection control. 2002; 30:411–416. [PubMed: 12410218]
31. Bassetti M, Cruciani M, Righi E, et al. Antimicrobial use and resistance among Gram-negative bacilli in an Italian intensive care unit (ICU). J Chemother. 2006; 18:261–267. [PubMed: 17129836]
32. Park S, In Y, Suh GY, et al. Evaluation of adverse drug reactions in medical intensive care units. European journal of clinical pharmacology. 2012
33. Engels DR, Evans GA, McKenna SM. Effect on duration of antimicrobial therapy of removing and re-establishing an automatic stop date policy. Can J Hosp Pharm. 2004; 57:214–219.
34. Toth NR, Chambers RM, Davis SL. Implementation of a care bundle for antimicrobial stewardship. Am J Health Syst Pharm. 2010; 67:746–749. [PubMed: 20410551]

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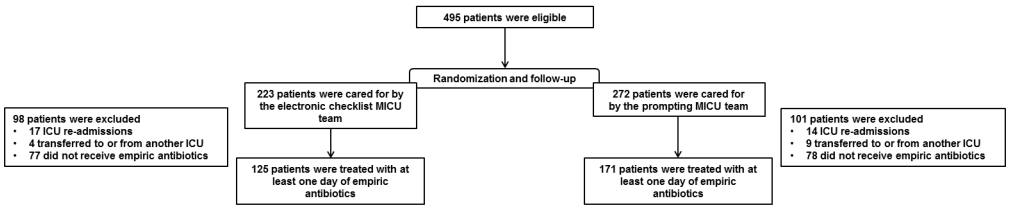

Figure 1.
Patient flowchart based on CONSORT diagram.

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Table 1

Baseline characteristics of study patients.

Characteristic	Electronic checklist (N=125)	Prompted (N=171)
Age (years), mean (SD)	62.6 (17.6)	60.0 (17.8)
Gender (male), no. (%)	66 (52.8)	88 (51.5)
Race, no. (%)		
White	52 (42.3)	80 (47.9)
African American	36 (29.3)	44 (26.4)
Hispanic	11 (8.9)	17 (10.2)
Asian	2 (1.6)	5 (3.0)
Other or declined	22 (17.9)	21 (12.6)
Location prior to MICU, no. (%)		
Emergency Department	67 (54.0)	92 (53.8)
General medical ward	53 (42.7)	64 (37.4)
Outside hospital transfer	4 (3.2)	15 (8.8)
Diagnosis, no. (%)[a,b]		
Sepsis	36 (29.0)	66 (38.6)
Pneumonia	29 (23.4)	31 (18.1)
Obstructive airways disease	4 (3.2)	9 (5.3)
Other respiratory[c]	17 (13.7)	12 (7.0)
GI hemorrhage	5 (4.0)	4 (2.3)
Metabolic	8 (6.5)	1 (0.6)
Neurologic	2 (1.6)	8 (4.7)
Drug intoxication/withdrawal	1 (0.8)	5 (2.9)
Other	22 (17.7)	35 (20.5)
Diagnosis, no. (%)[a,d]		
Sepsis or pneumonia	65 (52.4)	97 (56.7)
All other diagnoses	59 (47.6)	74 (43.3)
Sepsis sub-diagnosis, no. (%)[a]		

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Characteristic	Electronic checklist (N=125)	Prompted (N=171)
Pulmonary	5 (13.9)	18 (27.3)
GI	1 (2.8)	4 (6.1)
Urinary	10 (27.8)	9 (13.6)
Soft Tissue	4 (11.1)	7 (10.6)
Other or unknown	16 (44.4)	28 (42.4)
Mechanical ventilation within 24 hours of ICU admission, no. (%)	49 (39.5)	56 (32.8)
Hospital discharge disposition among survivors, no. (%)[e]		
Home	81 (85.3)	104 (74.3)
Skilled nursing or rehabilitation facility	10 (10.5)	30 (21.4)
Long-term acute care hospital	2 (2.1)	5 (3.6)
Short-term acute care hospital	2 (2.1)	1 (0.7)
APACHE IV predicted LOS, days[f]	5.6 (1.5)	5.6 (1.7)
APACHE IV predicted mortality, no. (%)[f,g]	42.8 (34.2)	46.7 (27.5)

[a] Diagnoses, including sepsis sub-diagnoses, are adapted from the APACHE IV prediction models.[19, 20]

[b] P=0.012 (Fisher's exact).

[c] Includes ARDS, pulmonary hemorrhage/hemoptysis, pleural effusion, respiratory arrest, lung cancer, sleep apnea, and non-specified respiratory diagnoses.

[d] P=0.46.

[e] P=0.085 (Fisher's exact).

[f] Missing data: one patient.

[g] P=0.043.

Crit Care Med. Author manuscript; available in PMC 2014 November 01.

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Table 2

Primary outcomes.

Outcome	Electronic checklist (N=125)	Prompted (N=171)	*P* Value
Patient-days on which empirical antibiotics were used, no. (%)	498/711 (70.0)	702/1112 (63.1)	0.002
Proportion of antibiotic-days on which empirical antibiotics were used, mean (SD)[a]	0.83 (0.27)	0.78 (0.27)	0.093
Empirical antibiotic duration (d), median [IQR]	3 [2–4]	3 [1–5]	0.27
Total antibiotic duration (d), median [IQR]	4 [2–8]	4 [2–7]	0.65

[a]Empiric antibiotic-days/total antibiotic-days.

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Table 3

Empirical antibiotic outcomes according to likelihood of infection.

Outcome	Definite/probable infection			Possible/empirical infection		
	Electronic checklist	Prompted	*P* value	Electronic checklist	Prompted	*P* value
Patient-days on which empirical antibiotics were used, no. (%)	46 (50.0)	65 (45.8)	0.53	452 (73.0)	637 (65.7)	0.002
Proportion of antibiotic-days on which empirical antibiotics were used, mean (SD)[a]	0.69 (0.34)	0.47 (0.22)	0.17	0.84 (0.26)	0.81 (0.26)	0.24
Empirical antibiotic duration (d), median [IQR]	3 [2–4]	3 [1–5]	0.38	3 [2–4.5]	2 [1–7]	0.41

[a]Empiric antibiotic-days/total antibiotic-days.

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Table 4

Clinical outcomes.

Outcome	Electronic checklist (N=125)	Prompted (N=171)	*P* value
ICU LOS, days	2.8 [1.7–6.5]	2.6 [1.5–6.9]	0.27
Hospital LOS, days	9.6 [5.9–15.8]	11.8 [5.9–22.8]	0.18
Hospital mortality, no. (%)	30 (24.0)	30 (17.5)	0.17
SMR (95% CI)[a]	0.70 (0.47–1.0)	0.64 (0.43–0.92)	
Adjusted odds of death (95% CI)[b]	Reference	0.90 (0.47–1.7)	0.75
Ventilator-free and alive at day 28, days	20.3 [0–25.9]	21.9 [13.5–25.7]	0.36

[a]Observed/APACHE IV predicted mortality. P<0.05 for comparisons with SMR=1.0.

[b]Adjusted for APACHE IV predicted mortality, ICU admission diagnosis.