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Background: Methicillin-resistant *Staphylococcus aureus* (MRSA) is responsible for the largest number of invasive infections due to a multidrug-resistant pathogen. Approximately 10% of hospitalized carriers will experience invasive MRSA disease in the year following discharge incurring antibiotic therapy beyond focused treatment of MRSA. **Objective:** We aimed to quantify the extent of non-MRSA empiric antibiotics incurred by MRSA infections and further assess the risk of *Clostridioides difficile* Infection (CDI) as a result of treatment of MRSA infection. **Methods:** The CLEAR Trial was a postdischarge randomized controlled trial of 2,121 MRSA carriers comparing MRSA education alone to education plus repeated decolonization that demonstrated a 30% reduction in MRSA infection and a 17% reduction in all-cause infection attributable to decolonization in the year following hospital discharge (Huang SS, *NEJM* 2019). We included all hospitalization outcomes due to MRSA infection in the CLEAR Trial with detailed medication administration records to quantify unintended consequences of MRSA infection related to empiric non-MRSA antibiotic use and resultant CDI. Full-text medical records were reviewed with a standardized abstraction form to collect inpatient administered antibiotics and hospital-associated CDI. **Results:** In total, 154 hospitalizations due to MRSA infection with a mean length-of-stay of 10.6 days were identified. During 25 hospitalizations (16.2%), patients received only anti-MRSA antibiotics. During the remaining 129 (83.8%) hospitalizations, patients received a mean of 1.6 distinct non-MRSA antibiotics totaling a mean of 6.6 days of therapy (DOT). Empiric non-MRSA therapy was given for 3.2 DOT before MRSA culture results became available and was continued for an additional 3.4 DOT afterward. Among all 849 non-MRSA DOT, the most common were due to piperacillin-tazobactam (293 DOT, 34.5%), levofloxacin (105 DOT, 12.4%), and metronidazole (93 DOT, 11.0%). Across all 154 hospitalizations, a mean of 5.5 non-MRSA DOT was calculated per MRSA hospitalization, with 6 CDI cases (3.9%) as a direct sequelae of empiric non-MRSA antibiotics provided for MRSA infection. **Conclusions:** Hospitalization for MRSA infection results in extensive non-MRSA empiric antibiotic therapy both before and after MRSA culture results are known. This antibiotic use is associated with a 3.9% risk of CDI that exceeds the national risk of acquiring CDI (3.2 per 1,000 admissions) by 12-fold during any hospital stay (Barrett ML, *AHRQ* 2018). The CLEAR Trial findings that post-discharge decolonization reduces MRSA infection and hospitalization by 30% suggests that decolonization may also reduce non-MRSA antibiotic use and CDI in this population.

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Update on Improving Outpatient Antibiotic Use Through Implementation and Evaluation of Core Elements of Outpatient Antibiotic

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Background: Acute respiratory infections (ARIs) are a key target to improve antibiotic use in the outpatient setting. The Core Elements of Outpatient Antibiotic Stewardship provide a framework for improving antibiotic use, but data on safety and effectiveness of interventions to improve antibiotic use are limited. We report the impact of Core Elements implementation within Veterans' Healthcare Administration clinics on antibiotic prescribing and patient outcomes. **Methods:** The intervention targeting treatment of uncomplicated ARIs (sinusitis, pharyngitis, bronchitis, and viral upper respiratory infections [URIs]) in emergency department and primary care settings was initiated within 10 sites between September 2017 and January 2018. The intervention was developed using the Core Elements and included local site champions, audit-and-feedback with peer comparison, and academic detailing. We evaluated the following outcomes: per-visit antibiotic prescribing rates overall and by diagnosis; appropriateness of treatment; 30-day ARI revisits; 30-day infectious complications (eg, pneumonia); 30-day adverse medication effects; 90-day *Clostridium difficile* infection (CDI); and 30-day hospitalizations. Multilevel logistic regression was used to calculate rate ratios (RR) with 95% CI for each outcome in the postintervention period (12 months) compared to the preintervention period (39–42 months). **Results:** There were 14,020 uncomplicated ARI visits before the intervention and 4,866 uncomplicated ARI visits after the intervention. The proportions of uncomplicated ARI visits with antibiotics prescribed were 59.17% before the intervention versus 44.34% after the intervention. A trend in reduced antibiotic prescribing for ARIs throughout the entire (before and after) observation period was evident (0.92; 95% CI, 0.90–0.94); however, a significant reduction in antibiotic prescribing after the intervention was identified (0.74; 95% CI, 0.59–0.93). Per-visit antibiotic prescribing rates decreased significantly for bronchitis and URI (0.54; 95% CI, 0.44–0.65), pharyngitis (0.76; 95% CI, 0.67–0.86), and sinusitis (0.92; 95% CI, 0.85–1.0). Appropriate therapy for pharyngitis increased (1.43; 95% CI, 1.21–1.68), but appropriate therapy for sinusitis remained unchanged (0.92; 95% CI, 0.85–1.0) after the intervention. Complications associated with antibiotic undertreatment were not different after the intervention: ARI-related revisit rates (1.01; 95% CI, 0.98–1.05) and infectious complications (1.01; 95% CI, 0.79–1.28). A potential benefit of improved antibiotic use included a reduction in visits for adverse medication effects (0.82; 95% CI, 0.72–0.94). Furthermore, 90-day CDI events were too sparse to model: preintervention incidence was 0.08% and postintervention incidence was 0.06%. Additionally, 30-day hospitalizations were significantly lower in the postintervention period (0.79; 95% CI, 0.72–0.87). **Conclusions:** Implementation of the Core Elements was safe and effective and was associated with reduced antibiotic prescribing rates for uncomplicated ARIs, improvements in diagnosis-specific appropriate therapy, visits for adverse antibiotic effects, and 30-day hospitalization rates. No adverse events were noted in ARI-related revisit rates or infectious complications. CDI rates were low and unchanged.

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