Impact of Resistance Thresholds on Mortality in Hospital-Acquired and Ventilator-Associated Pneumonia

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ABSTRACT # 1478

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Background

Hospital-acquired (HAP) and ventilator-associated pneumonia (VAP) represent a significant source of morbidity and mortality in hospitalized patients. Numerous studies demonstrate mortality benefit with appropriate empiric therapy. Choosing the right empiric coverage is paramount; however, this decision becomes more challenging as rates of antibiotic resistance rise. Most recent HAP/VAP guidelines use an arbitrary population resistance rate of 20% to recommended methicillin-resistant *Staphylococcus aureus* (MRSA) coverage and double-coverage of resistant gram-negative bacilli (GNB). Using this threshold has led to overuse of broad-spectrum antimicrobials. The goal of this study is to mathematically explore the impact of this threshold on patient outcomes and link population resistance rates to individual mortality risk.

Methods

We used the concept of excess mortality risk (EMR) to develop a theoretical simulation model based for HAP/VAP caused by GNB and MRSA empirically treated with piperacillin-tazobactam and vancomycin. EMR is the product of the proportion of HAP/VAP caused by GNB/MRSA, the rate of antibiotic (piperacillin-tazobactam/ methicillin) resistance in GNB and Staphylococcus aureus isolates and the difference in mortality between discordant and appropriate antibiotic therapy. Model parameters were obtained from large surveillance networks and published clinical trials.

Results

At the HAP/VAP guideline threshold of 20% methicillin resistance in SA isolates, the EMR was 0.3%; when the model included only culture positive patients, EMR was 0.6%. At a threshold of 20% resistance to piperacillin-tazobactam in GNB isolates, EMR was 1.9% and 3.1% when culture-negative patients were excluded. EMR increased as baseline risk of failure with discordant therapy increased (e.g. critically ill patients, ventilated HAP).

Conclusion

This model offers a mathematical exploration of the individual excess risk for death in patients with HAP/VAP caused by GNB/MRSA because of discordant therapy. The objectivity of the model would better allow clinicians, guideline authors, and health policy makers to weigh excess risk versus possible harms of broad-spectrum therapy when developing population resistance thresholds cutoffs for empiric therapy recommendations.

BACKGROUND

- **HAP is defined as an infection of the parenchyma of the lung developing >48 hours after admission to the hospital. A subset of these infections in patients requiring mechanical ventilation >48 hours are designated as VAP.**
- **Prompt administration of antibiotics with activity against the culprit pathogen is associated with lower mortality in HAP/VAP.[1,2]**
- **Though they contain several material differences, both USA and European HAP/VAP guidelines make recommendations regarding empiric antibiotic therapy based on prevalence of MDR pathogens in local populations. The thresholds to initiate empiric MDR pathogen coverage ranges from 10% for *Pseudomonas aeruginosa* in the IDSA guidelines to 25% for GNB/MRSA in the ECSMID guidelines.[3,4]**
- **Population-level parameters are easily applied to guidelines and treatment-algorithms, though do not provide clear insight into individual patient outcomes. Our study applies a mathematical model to explore these patient outcomes.**

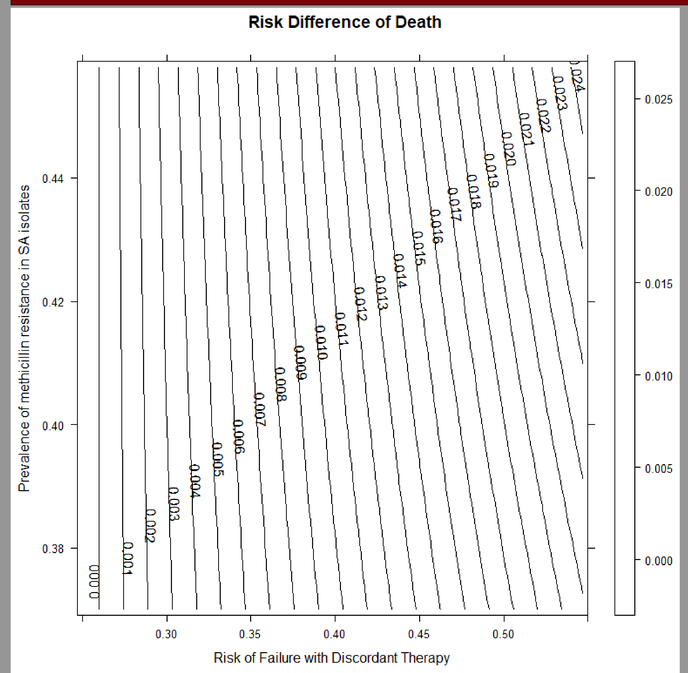
METHODS

- **The following formula was used to calculate EMR**

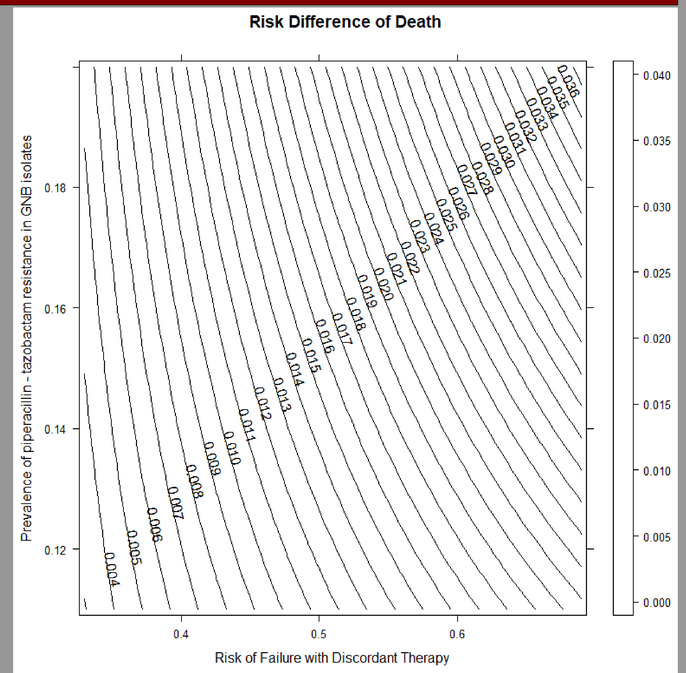
$$EMR = PR \times RR \times \Delta mortality$$

- **PR is the prevalence rate of the culprit pathogen in HAP/VAP diagnoses**
- **RR is the rate of antibiotic resistance (oxacillin for *S. aureus* and piperacillin/tazobactam for GNB)**
- **Δmortality is the difference in mortality between discordant and appropriate antibiotic therapy**
- **Variable information was obtained from the following sources:**
  - **Prevalence obtained from SENTRY and NHSN databases**
  - **Culture negativity and outcome data obtained from ASPECT-NP trial, REPROVE trial, and Sader, et al 2014.**
- **Two iterations of the model was performed. One analysis included all HAP/VAP cases, and the other only included cases with positive cultures identifying a culprit pathogen.**

RESULTS



- **Prevalence of *S. aureus* for HAP/VAP and probability of clinical failures**
  - ***S. aureus* as culprit pathogen: 24-29.8%**
    - **Resistant to Oxacillin: 37-45.8%**
    - **Failure with optimal antibiotic therapy 16.5-37.1%**
    - **Failure with discordant antibiotic therapy: 19.3-54.7%**



- **Prevalence of GNB for HAP/VAP and probability of clinical failures**
  - **GNB as culprit pathogen: 36.1-44.7%**
    - **Resistant to piperacillin/tazobactam: 11.1-21.9%**
    - **Failure with optimal antibiotic therapy: 7.9-47.6%**
    - **Failure with discordant antibiotic therapy: 33.3-69.7%**

ANALYSIS

- **Using the 20% antibiotic resistance prevalence threshold, our model found the EMR for culture positive HAP/VAP patients was 0.6% and 3.1% for MRSA and MDR GNB, respectively.**
- **When the model was run including culture negative HAP/VAP cases, the EMR was 0.3% for MRSA and 1.9% for MDR GNB.**
- **When applied to literature prevalence rates for methicillin-resistance in *S. aureus* isolates of 37-45.8% and MDR GNB prevalence rates of 11.1-21.9%, EMR benefit did not exceed 2.4% or 3.6%, respectively, even at the extreme of antibiotic failure risk.**
- **Though prevalence thresholds for empiric antibiotic coverage appear to be reasonable, the mathematical estimation of excess mortality risk for an individual was lower than the authors expected.**
- **The results of our EMR analysis are consistent with a 2020 retrospective cohort study of 88,605 patients that did not find a mortality benefit for empiric anti-MRSA antibiotics in patients hospitalized for pneumonia.[8]**

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CONCLUSIONS

- **Our model provides an objective estimation of the effect of empiric antibiotic therapy on mortality of patients diagnosed with HAP/VAP**
- **This proposed EMR model should be further validated in additional real-world patient populations. If validated, it would feasible to use expected individual EMR thresholds for empiric antibiotic recommendations. Ideally, local prevalence rates and antibiograms could be utilized as input variables to get estimated EMR in a specific institution.**
- **Additionally, an objective measure of expected benefit of empiric therapy would provide context for development of guideline recommendations for empiric antibiotic regimens.**

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