Can Electronic Decision Support Tools Really Reduce Mortality from Community-acquired Pneumonia?

Reported mortality rates from community-acquired pneumonia (CAP) have changed very little in the past few decades. Although the addition of macrolides as part of combination antibiotic therapy appears to have had a significant positive effect in severe pneumonia (1), the only other intervention with strong evidence for a beneficial effect is more timely administration of antibiotics, preferably within 4 hours of presentation (1). The failure to improve unadjusted mortality rates from pneumonia is in part a failure to develop new therapies but is also a reflection of an increasingly aged, multimorbidity population acquiring pneumonia having higher predicted mortality at presentation (2). Reflecting the limited avenues for improving outcomes from CAP, analyses of mortality have failed to identify any modifiable factors in most patients (3, 4).

In this issue of the *Journal*, Dean and colleagues (pp. 1330–1336) report their results from the deployment of an electronic clinical decision support tool (ePNa) across 16 community hospitals in Utah and California (5). The ePNa builds on previous work from the investigators (6) and aims to provide standardized guidance around the diagnosis, risk stratification, microbiology studies, site of care, and antibiotic therapy in the setting of CAP.

The authors used a novel step-wedged cluster trial design that involved sequential crossover of geographic clusters of 16 hospitals at 2-month intervals. The design is an approach for investigating changes to clinical care that are mandatory on ethical grounds or necessitated by improvements in technology. The intervention could not be blinded and may have been confounded by temporal changes in the treatment of pneumonia. Although, the authors adjusted for secular trends by including the ePNa implementation time as a fixed effect and performed several sensitivity analyses. The selection of clusters was not random, and it is possible that bias arose from the vanguard four cluster comprising the larger intermountain hospitals, whereas the last two clusters contained smaller rural hospitals whose fewer patients had less influence. The trial was registered with a single primary outcome, and it was powered to detect a 2% fall in mortality with 9,370 subjects; however, 6,848 subjects were needed to show a significant fall of 3.8% (from 8.6% before to 4.8% after deployment). The odds ratio for 30-day mortality after adjustment for severity of illness was 0.62 (95% confidence interval, 0.49–0.79; $P < 0.001$).

The trial methodology is possibly not perfect, but the finding is a stunning reduction in mortality that would justify worldwide adoption of the ePNa. There are, however, a number of important caveats with this study that necessitate further research be done before an ePNa is adopted as a standard of care. With respect to the before and after deployment cohorts, there are substantial differences between the baseline characteristics that need to be considered. A difference of 5 years in mean age is clinically significant, as is a 3% difference in predicted mortality based on electronic CURB (Confusion, Urea, Respiratory rate, Blood pressure). The higher prevalence of chronic renal disease (31% vs. 23%) and chronic heart disease (35% vs. 27%) further creates a picture of a more severe cohort of patients at baseline in the predeployment cohort. Although the multivariate analysis was performed to adjust for all these factors, it is hard to escape a view that most, but not all, of the improved mortality observed was because of differences in baseline factors.

Equally important in accepting that an ePNa reduces mortality is explaining how it does so, acknowledging it may impact through a variety of different mechanisms. Dean and colleagues observed a 9-minute improvement in time to first antibiotics; however, although it is statistically significant, it is hard to imagine this had a clinically significant impact. Guideline-concordant therapy did improve with ePNa (from 79.5% to 87.9%), mostly through reduced use of inappropriately broad-spectrum antibiotics. Because the use of inappropriate empiric antipseudomonal and antimethicillin resistant *Staphylococcus aureus* antibiotics has been associated with no improvement (7, 8) and possibly worse outcomes in patients with CAP (9), this is certainly one believable mechanism by which ePNa may be improving outcomes. Reducing the use of these antibiotics was the driver behind the recent American Thoracic Society and Infectious Diseases Society of America CAP guidelines (10) to move away from the concept of healthcare-associated pneumonia.

Other studies aimed at improving the process of care for patients with CAP have demonstrated improved degrees of outpatient care but not reduced mortality (11, 12). Earlier, appropriate triage to intensive care might alter patient outcomes (13), but this was not demonstrated as a benefit of the ePNa by Dean and colleagues. Increased appropriate use of microbiological tests was part of the ePNa; however, although performing blood cultures has been associated with better patient outcomes, given the evidence that these rarely directly influence patient treatment, it is more likely that they represent adherence to a general package of care rather than directly affect patient outcome. Greater use of macrolides in combination with β-lactams is also associated with better patient outcomes, especially in more severe disease (1); however, this was also not demonstrated to have occurred (5).

In conclusion, the claim that an ePNa can reduce mortality in CAP by nearly 40% cannot be ignored. However, quite a bit of work remains to determine which interventions drive the benefit seen with an ePNa, and to what extent, as this will enable refinement of the tool for maximum benefit. ■

Originally Published in Press as DOI: 10.1164/rccm.202202-0358ED on March 23, 2022

Author disclosures are available with the text of this article at www.atsjournals.org.

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Monocyte Activation: The Link between Obstructive Sleep Apnea and Cardiovascular Disease?

Although obstructive sleep apnea (OSA) is an independent predictor of cardiovascular disease (CVD) (1), the underlying biological mechanisms mediating this relationship have remained elusive. One potential pathway may be via activation of circulating monocytes. Phenotypic markers of monocyte activation predict incident cardiovascular events above and beyond traditional CVD risk factors (2). Monocytes are increasingly recognized to play a key pathogenic role in the development of atherosclerosis, and the NLRP3 (Nod-like receptor protein 3) inflammasome plays a central role. Activation of the NLRP3 inflammasome stimulates monocytes to release IL-1β. IL-1β promotes surrounding immune and endothelial cells to secrete IL-6 and tumor necrosis factor-α and express vascular cell adhesion markers, which attract additional circulating monocytes to areas of vascular inflammation. These monocytes migrate across the vessel wall and differentiate into macrophages, whereupon, through engulfment of oxidized low-density lipoprotein, they develop into foam cells and contribute to atherosclerotic plaque formation (3). In addition, NLRP3 inflammasome activation leads to pyroptosis, a unique type of cell death, in which gasdermin-D induces cell permeability and lysis. This promotes further local inflammation through secretion of cytokines and microvesicles (4). Perhaps the most convincing evidence establishing a causal role of the NLRP3 inflammasome in CVD pathogenesis is that inhibition of IL-1β reduces recurrent cardiovascular events in patients with preexisting CVD (5).

Two steps are necessary in canonical NLRP3 inflammasome activation (6). First, priming of the pathway is triggered by activation of NF-κB (nuclear factor-κB) signaling, which induces production of

Supported by the American Thoracic Society Academic Sleep Pulmonary Integrated Research/Clinical Fellowship and NHLBI grant K12 HL143886.

Originally Published in Press as DOI: 10.1164/rccm.202201-0215ED on April 18, 2022