Oxygen Saturations Less than 92% Are Associated with Major Adverse Events in Outpatients with Pneumonia: A Population-Based Cohort Study

Sumit R. Majumdar,1,2 Dean T. Eurich,2 John-Michael Gamble,2 A. Senthilselvan,2 and Thomas J. Marrie3

1Department of Medicine, Faculty of Medicine and Dentistry and 2Department of Public Health Sciences, School of Public Health, University of Alberta, Edmonton, Alberta, Canada; 3Department of Medicine, Faculty of Medicine, Dalhousie University, Halifax, Nova Scotia, Canada

Background. Patients with hypoxemia (blood oxygen saturation <90%) are usually hospitalized, although validated criteria (eg, the Pneumonia Severity Index [PSI]) suggest outpatient treatment is safe. We sought evidence to support or refute the practice.

Methods. All patients in Edmonton, Alberta, Canada with pneumonia assessed at any of 7 emergency departments (EDs) and then discharged were enrolled in a population-based cohort study. The independent variable of interest was oxygen saturation; the outcome was the composite endpoint of 30-day mortality or hospitalization.

Results. The study evaluated 2923 individuals with pneumonia who were treated as outpatients at any of 7 EDs. The patients’ mean age (standard deviation [SD]) was 52 (20) years; 47% were women; 74% were low risk (PSI Class I–II). The mean blood oxygen saturation (SD) was 95% (3%); 126 patients (4%) had blood oxygen saturations <90%, and 201 patients (7%) had blood oxygen saturations of 90%–92%. Over 30 days, 39 patients (1%) died and 252 (9%) reached the composite endpoint. Compared with patients with higher blood oxygen saturations, those discharged with saturations <90% had significantly (P < .001) higher rates of 30-day mortality (7 [6%] vs 32 [1%]), hospitalization (23 [18%] vs 201 [7%]), and composite endpoints (27 [21%] vs 225 [8%]). Blood oxygen saturation <90% was independently associated with 30-day mortality or hospitalization (adjusted odds ratio [OR], 1.7; 95% confidence interval [CI] 1.1–2.8; P = .032). If the saturation threshold for hospitalization was 92%, then there was no association with adverse events (adjusted OR 1.1, 95% CI 0.8–1.7, P = .48). Raising the admission threshold to 92% entails 1 additional hospitalization for every 14 patients discharged.

Conclusions. Among outpatients with pneumonia, oxygen saturations <90% were associated with increased morbidity and mortality. Our results indicate a hospital admission threshold of <92% would be safer and clinically better justified.

Community-acquired pneumonia is a common condition, and in the United States it is, with influenza, the 8th most common cause of death and the most common cause of infection-related death [1]. In the United States alone, approximately $10 billion is spent each year to manage about 4 million episodes of, and almost 1 million hospitalizations for, pneumonia [2]. Although most episodes of pneumonia are managed on an outpatient basis, much of the morbidity, mortality, and costs are associated with patients admitted to hospitals [1, 2]. Thus, the site-of-care decision is one of the most important aspects of managing pneumonia, and it is the most expensive [1, 2]. Much study has been devoted to using clinical and laboratory findings at presentation to predict which patients with pneumonia are at highest risk of short-term mortality and would benefit from admission to the hospital for more aggressive care and support [3–6]. Several risk-stratification tools have been developed, most notably the SMART-COP [4], CURB-65 [5], and the Pneumonia Severity Index (PSI) [6].
Randomized trials have demonstrated that the PSI can distinguish between low-risk (less than 1% risk of 30-day mortality) and high-risk patients with pneumonia and safely increase the proportion treated as outpatients [7–9]. Nevertheless, even with risk stratification tools, many physicians still admit “predicted low-risk” patients to hospital [6, 10, 11]. Why? The most common reason to admit a low-risk patient with pneumonia to hospital is hypoxemia [10, 11]. It is noteworthy that hypoxemia was an exclusion criterion in the randomized trials evaluating the use of the PSI [7–9] and it has been associated with an odds ratio of 173 for hospital admission [10].

Hypoxemia, conventionally defined as an oxygen saturation <90% or a PaO2 <60 mm Hg, is considered by physicians [10, 11], clinical experts [2], and researchers [6–9] to be a stand-alone criterion for admission. The same definition of hypoxemia is a validated marker of clinical instability for hospitalized patients and a stand-alone criterion for delaying discharge [12]. We have not found any empiric evidence to support or refute the safety and effectiveness of treating hypoxic patients with pneumonia as outpatients. Any evidence to help inform this issue would have important clinical and policy implications. Therefore, we undertook this study to examine 30-day outcomes for those with pneumonia and hypoxemia who were treated as outpatients. In addition, we wanted to determine if there might be a more appropriate (either higher or lower) oxygen saturation threshold to help guide the hospital admission decision for pneumonia.

METHODS

Setting and Participants
From 2000–2002, all patients with pneumonia evaluated in any of the 7 emergency departments (EDs) serving Edmonton, Alberta, Canada, were enrolled in a population-based clinical registry. The greater metropolitan Edmonton region has a population of more than 1 million people cared for by more than 1000 physicians working at 6 hospitals and has an annual healthcare budget of almost 2 billion dollars.

The details and concurrent analyses of more than 3000 patients with pneumonia seen at these 7 EDs and subsequently admitted to hospital have been previously published [13–15]. For this study, all 3344 adults with pneumonia (defined as 2 or more symptoms or signs [cough; pleurisy; shortness of breath; temperature >38°C; crackles or bronchial breathing on auscultation] plus radiographic evidence of pneumonia as interpreted by treating physicians) seen and evaluated in the ED and then discharged for outpatient treatment were included. Other than hospital admission, the only exclusion criteria were tuberculosis, cystic fibrosis, immunocompromised status, or pregnancy. All patients were treated according to a validated clinical pathway that had triage and site-of-care suggestions based on the PSI and recommendations for investigations and guideline-concordant antibiotics [7]. The study was approved by the institutional ethics review board of the University of Alberta (Edmonton, Alberta, Canada).

Data Collection and Measurements
Research nurses prospectively and independently collected clinical, functional status and laboratory data. For pragmatic reasons data collection was more limited than for our inpatient cohort [13–15]. For example, we did not collect all chronic medications and most laboratory values were dichotomized and collected as abnormal vs not based on PSI criteria. The PSI, an exhaustively validated tool designed to predict 30-day all-cause mortality in patients with pneumonia has also been used for risk adjustment [3, 6, 15], and was calculated at the point of care (see Supplementary Appendix).

The general approach to triage outlined in our pathway suggested that any patient with a PSI score >90 (Class IV or V) or any patient the ED physician judged needed hospital admission was referred to a hospitalist physician—and the remainder could be treated as outpatients and discharged home. Antibiotic treatment recommendations were classified as guideline-concordant (ie, respiratory fluoroquinolones, macrolide monotherapy, macrolides combined with β-lactams, or doxycycline) or not.

Oxygen Saturation
By protocol, blood oxygen saturation was measured by pulse oximetry performed on room air at the time of presentation. Serial measures may have been undertaken, and oxygen saturations by arterial blood gas may have also been collected, but we restricted analyses to the first oxygen saturation measurement because this was most consistently reported (and usually the only measurement that was actually recorded), most clinically relevant, and most often used for decision-making in the ED and other outpatient settings. By convention, saturations <90% represented hypoxemia [2–12]. We also categorized oxygen saturation as follows: <88%, 88–89.9, 90–91.9, 92–93.9, and ≥94%.

Outcomes
We elected to use the composite endpoint of 30-day all-cause mortality or all-cause hospitalization as our primary outcome because it is a clinically meaningful measure of safety and effectiveness that captures both morbidity and mortality [12, 16]. This composite outcome represents major adverse events and it is commonly used in studies of many conditions including pneumonia [12, 16]. If someone both was hospitalized and died within 30 days, the patient contributed only 1 event to the composite endpoint. To ascertain longer-term outcomes, we linked patients to provincial administrative databases that included vital statistics and health-resource use by using each patient’s unique personal health number. The rate of successful linkage between population-based clinical registries and our
Analysis
Patient characteristics were initially stratified according to mutually exclusive categories of blood oxygen saturation. Analysis of variance or $\chi^2$ tests, as appropriate, were used to examine the distribution of patient characteristics according to levels of oxygen saturation. We plotted outcomes against oxygen saturation using locally weighted scatterplot smoothing (Lowess) curves.

Multiple logistic regression was used to determine the independent association between hypoxemia (blood oxygen saturation $<90\%$) and our composite outcome. Because the PSI already includes age, we did not adjust for this separately in our models. The PSI also includes hypoxemia ($P_02 < 60$ mm Hg or blood oxygen saturation $<90\%$) but accords it only 10 points [6], so we subtracted this value from hypoxemic patients (see Supplementary Appendix). We forced oxygen saturation (dichotomous variable) and the modified PSI (continuous variable) into all models. We then considered other variables based on clinical importance, univariate $P$ values $<.1$, or when a variable confounded (>10% change in $\beta$) the association between saturation and outcomes irrespective of statistical significance. No first-order interaction terms achieved statistical significance. No first-order interaction terms achieved statistical significance. No first-order interaction terms achieved statistical significance.

We undertook several sensitivity analyses. First, we reanalyzed our data using different saturation thresholds—our main goal was to determine whether there was a threshold at which oxygen saturation was no longer independently associated with major adverse events. Second, we undertook a series of restriction analyses. Specifically, we reran analyses after excluding: (1) patients with severe pneumonia (PSI $>90$), because they are at very high risk of death and ought to have been admitted under almost all circumstances; (2) patients with chronic obstructive pulmonary disease (COPD), because these patients tend to have baseline hypoxemia and because it is often difficult to distinguish pneumonia from COPD exacerbation; and (3) patients whose pneumonia was not confirmed by a board-certified radiologist, because many authorities still do not agree that a diagnosis of pneumonia can be made without an abnormal chest radiograph [13]. Analyses were conducted using Stata-SE version 11 (StataCorp LP, College Station, TX).

RESULTS
Over 2 years, a total of 3344 people with pneumonia were seen in 7 regional EDs and treated on an outpatient basis. Of these patients, 237 (7%) could not be linked to administrative databases for outcome ascertainment and 184 (6%) did not have oxygen saturation measured. The remaining 2923 patients constituted our final study cohort. The mean (standard deviation[SD]) age was 52 (20) years, 47% were women, 5% were from nursing homes, and most (74%) were considered to have very low-risk pneumonia (PSI $<70$, Class I and II). For some common indicators of the quality of pneumonia care, 100% of patients had a chest radiograph, 96% received guideline-concordant antibiotic treatments and 94% had their oxygen saturation measured. The mean oxygen saturation (SD) of the study cohort was 95% (3%). Of the 2923 patients, 50 (2%) had an oxygen saturation $<88\%$; 126 (4%) had $<90\%$; and 327 (11%) had $<92\%$. In general, as oxygen saturations decreased, age, comorbidity, functional status, and pneumonia severity all increased (Table 1).

Mortality and Hospitalization
Thirty days after the initial visit to the ED, 39 of the 2923 outpatients (1%) had died, and 224 (8%) were hospitalized; in all, 252 (9%) reached the composite outcome of death or hospitalization. Most deaths (28 of 39 [72%]) occurred outside of the hospital setting, either at home (23 of 28) or during a subsequent ED visit (5 of 28). There was an inverse linear relationship between blood oxygen saturation and major adverse events, with no inflection at the conventional definition of hypoxemia, blood oxygen saturation of 90% (Figure 1). Compared with those with higher blood oxygen saturations, patients discharged with saturations $<90\%$ had greater 30-day mortality (7 of 126 [6%] vs 32 of 2797 [1%]; $p < .001$), hospitalization (23 [18%] vs 201 [7%]; $P < .001$), and composite outcomes (27 [21%] vs 225 [8%]; $P < .001$) (Figure 2).

Multiple Logistic Regression Analysis
In analyses adjusted for pneumonia severity, confirmation by chest radiograph, and receipt of guideline-concordant antibiotics, an oxygen saturation $<90\%$ was still independently associated with increased rates of 30-day mortality or hospitalization (adjusted odds ratio [OR] 1.7; 95% confidence interval [CI], 1.1–2.8; $P = .032$ [Table 2]). The adjusted OR for blood oxygen saturations $<90\%$ were also increased for the individual endpoints of 30-day mortality (2.0; 95% CI, 0.7–5.4; $P = .17$) and hospitalization (1.7; 95% CI, 1.1–2.9; $P = .030$).

Sensitivity Analyses
In examining commonly used thresholds for oxygen saturation, we found that only when the cut point was 92% was there no longer any independent association with the composite outcome of 30-day mortality or hospitalization (adjusted OR, 1.1; 95% CI, 0.8–1.7; $P = .48$). Similarly, when oxygen saturations were $\geq 92\%$, we found no significant association with either mortality alone (adjusted $P = .8$) or hospitalization alone (adjusted...
P = .3) within 30 days (Figure 2). Raising the admission saturation threshold from 90% to 92% would have resulted in another 201 (7%) hospitalizations. Thus, 1 of every 14 patients in our study would have been admitted to the hospital instead of discharged home for outpatient treatment.

For our restriction analyses, all point estimates for the association between oxygen saturation <90% and major adverse events increased in magnitude and all but one remained statistically significant. Specifically, when we excluded 341 (12%) patients with severe pneumonia (PSI > 90), the adjusted OR was 2.3 (P = .011); when we excluded 245 (8%) patients with COPD, the adjusted OR was 2.2 (P = .007); and when we excluded 1544 (53%) patients who did not have radiograph confirmation of pneumonia, the adjusted OR was 1.9 (P = .108).

**DISCUSSION**

In a population-based cohort of nearly 3000 people with pneumonia managed according to a validated clinical pathway and discharged home to be treated as outpatients, we documented that 30-day rates of death or subsequent hospitalization were almost 10%. This finding was primarily a result of patients eventually returning to the ED and being admitted to hospital, but even 30-day mortality was 1%. We also found that hypoxemia defined as blood oxygen saturation <90% was associated with a statistically significant 70% increase (adjusted OR 1.7; P = .032) in 30-day mortality or hospitalization. This increased
risk of major adverse events was independent of disease severity and appropriate antibiotic treatment. Our results validate the clinical weight that most physicians place on the presence of hypoxemia when it comes to making site-of-care decisions for cases of pneumonia [6, 10, 11, 18].

This study is unique in its attempt to document the risks associated with hypoxemia in a population-based sample of patients with pneumonia treated outside of the hospital. A previous study by Levin et al attempted to examine this issue. In a highly selected cohort of 944 outpatients drawn from 5 sites in the United States and Canada in the early 1990s, they reported that only 21% even had their oxygen saturations measured. Of the 198 outpatients with oxygenation assessments examined, the mean blood oxygen saturation on room air was 96%, and 4% of patients had hypoxemia—results identical to those we report. However, perhaps because of the very small sample size, Levin et al did not analyze or report 30-day outcomes for outpatients with hypoxemia [18].

Strengths and Limitations

Strengths of this research include that it was population-based and relatively large; it had clinical information; and patients were treated in a standardized manner. Nevertheless, there are several important limitations to this nonrandomized study. First, our measures of blood oxygen saturation were based on pulse oximetry and not arterial blood gases. The former, but not the latter, can be affected by nail polish, motion artifact, hypoperfusion, or severe hypoxemia [18]. Nonetheless, it is oxygen saturation measured by pulse oximetry that is widely available for clinical decision-making—and not the more invasive and expensive arterial blood gas tests—so much so that saturation measured by pulse oximetry is considered the “fifth” vital sign [18].

Second, our analyses were restricted to the oxygen saturation measured at presentation, and we do not know to what extent patients’ oxygenation may have improved during their ED stays. We also do not know to what extent patients’ oxygenation may have deteriorated before discharge. These 2 limitations would tend to bias the null, and they suggest that we have probably underestimated the potential risks associated with hypoxemia.

<table>
<thead>
<tr>
<th>Variables</th>
<th>&lt;90% Oxygen Saturation</th>
<th>P-value</th>
<th>&lt;92% Oxygen Saturation</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoxemia</td>
<td>1.70 (1.05–2.77)</td>
<td>.032</td>
<td>1.14 (0.79–1.66)</td>
<td>.50</td>
</tr>
<tr>
<td>Female</td>
<td>1.30 (1.00–1.74)</td>
<td>.053</td>
<td>1.30 (0.99–1.74)</td>
<td>.055</td>
</tr>
<tr>
<td>PSI score (per unit)</td>
<td>1.03 (1.03–1.04)</td>
<td>&lt;.001</td>
<td>1.03 (1.03–1.04)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Chest radiograph confirmation</td>
<td>1.30 (0.97–1.69)</td>
<td>.084</td>
<td>1.30 (0.97–1.69)</td>
<td>.078</td>
</tr>
<tr>
<td>Guideline concordant antibiotics</td>
<td>0.55 (0.33–0.92)</td>
<td>.22</td>
<td>0.55 (0.33–0.92)</td>
<td>.22</td>
</tr>
</tbody>
</table>

* Hosmer-Lemeshow goodness-of-fit test $P = .95$ for both presented models

Figure 2. Major Adverse Events in Outpatients with Pneumonia According to Different Oxygen Saturation Thresholds

Low oxygen saturation reflects an integrated noninvasive measure of the extent of lung parenchyma involvement by infection, consequent anatomic and physiologic derangements, and available cardiopulmonary functional reserve, and thus it seems to accurately capture the clinical severity of pneumonia. Indeed, most experts suggest that patients with pneumonia and hypoxemia should be admitted to the hospital for initial treatment and careful observation, and that an oxygen saturation < 90% is an “absolute contraindication” to outpatient treatment [2]. In our study, however, it was not until the admission-to-hospital threshold was raised to 92% that oxygen saturation was no longer significantly associated with short-term morbidity and mortality. Although a 2% shift upward in oxygen saturation may seem inconsequential, in absolute terms in our population it represented an additional 7% of outpatients being admitted to hospital. Thus, the number-needed-to-admit to “prevent or ameliorate” 1 major adverse event would be 14.

TABLE 2. Independent Correlates of 30-Day Mortality and Hospitalization in 2923 Outpatients with Pneumonia (Multiple Logistic Regression*)

Hypoxemia In Outpatients With Pneumonia • CID 2011:52 (1 February) • 329
Third, we considered all short-term mortality and hospitalizations to be pneumonia related. For such a short period as 30 days we (and others [5–9, 19]) considered this a reasonable assumption, and we did not attempt to attribute cause of death or reason for hospital admission to pneumonia vs other conditions. Similarly, we made no post hoc judgments on whether deaths or hospitalizations were preventable.

Fourth, we acknowledge we may have lost some statistical information because we chose to analyze common discrete clinical cut-points to examine oxygenation (ie, 90% or 92%) though saturation is a continuous physiologic variable [20]. Thus, we also assumed any of the potential benefits of hospitalizing patients with blood oxygen saturations <90% would generally accrue to patients hospitalized with better saturations between 90% and 92%. Beyond replicating our work in an independent population, the only way to authenticate our assumptions would be a (not particularly feasible) trial that uses a validated instrument [4–6] to stratify patients according to predicted risk of mortality and then randomizes those not admitted to the hospital using conventional criteria to admission decisions based on the first oxygen saturations measured.

Fifth, we do not know to what extent physicians wanted to admit patients to hospital relative to the degree or vehemence of preference expressed by patients to be treated on an ambulatory basis. Three-fourths of people with pneumonia prefer outpatient treatment if it is possible, and most are even willing to pay out-of-pocket for this option [21].

Last, some may be concerned about the generalizability of our conclusions. At the least, for community-acquired pneumonia it is well documented that etiologies, processes, and outcomes of care in Canada are nearly identical to those from multiple regions in the US [19].

CONCLUSIONS

In conclusion, we found that conventional wisdom is both correct and incorrect. It is correct in that we have verified that hypoxemia is a powerful and independent indicator of a substantially increased risk of 30-day morbidity and mortality for outpatients with pneumonia. It may be, however, incorrect in that the usual definition of hypoxemia of <90% is too low for making site-of-care decisions. Instead, our results suggest that as a single independent criterion for hospital admission, oxygen saturation <92% might be both safer and clinically better-justified for patients with pneumonia.

Acknowledgments

The corresponding author (S.R.M.) had full access to all the data in the study and had final responsibility for the decision to submit for publication. For their dedication and diligence, we would like to thank the Community-Acquired Pneumonia Pathway research nurses and EPICORE (University of Alberta) for data management.

Financial support. This work was supported by grants from the Canadian Institutes of Health Research (CIHR) (CIHR; MOP-191604); the Alberta Heritage Foundation for Medical Research (AHFMR); grants-in-aid from Capital Health and unrestricted grants from Abbott Canada; Pfizer Canada; and Janssen-Ortho Canada. S.R.M. receives salary support awards from AHFMR (Health Scholar); and D.T.E. from AHFMR (Population Health Investigator) and CIHR (New Investigator).

Potential conflicts of interest. All authors: no conflicts.

Authors’ Contributions. S.R.M. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the analysis. All authors participated in study design, analysis, interpretation, revisions, and approved the final manuscript. S.R.M. conceived the study, drafted the initial manuscript, and will act as guarantor and corresponding author. S.R.M., D.T.E., and T.J.M. obtained funding and supervised the study. All authors have seen and approved the final version.

Supplementary Material

Supplementary materials are available at Clinical Infectious Diseases online (http://www.oxfordjournals.org/our_journals/cid/).

Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

References


