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MAJOR ARTICLE

Diagnosis and Treatment of Pneumonia in Urgent Care Clinics: Opportunities for Improving Care

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Background. Community-acquired pneumonia is a well-studied condition; yet, in the urgent care setting, patient characteristics and adherence to guideline-recommended care are poorly described. Within Intermountain Health, a nonprofit integrated US health care system based in Utah, more patients present to urgent care clinics (UCCs) than emergency departments (EDs) for pneumonia care.

Methods. We performed a retrospective cohort study 1 January 2019 through 31 December 2020 in 28 UCCs within Utah. We extracted electronic health record data for patients aged ≥12 years with *ICD-10* pneumonia diagnoses entered by the bedside clinician, excluding patients with preceding pneumonia within 30 days or missing vital signs. We compared UCC patients with radiographic pneumonia (n = 4689), without radiographic pneumonia (n = 1053), without chest imaging (n = 1472), and matched controls with acute cough/bronchitis (n = 15 972). Additional outcomes were 30-day mortality and the proportion of patients with ED visits or hospital admission within 7 days after the index encounter.

Results. UCC patients diagnosed with pneumonia and possible/likely radiographic pneumonia by radiologist report had a mean age of 40 years and 52% were female. Almost all patients with pneumonia (93%) were treated with antibiotics, including those without radiographic confirmation. Hospital admissions and ED visits within 7 days were more common in patients with radiographic pneumonia vs patients with "unlikely" radiographs (6% vs 2% and 10% vs 6%, respectively). Observed 30-day all-cause mortality was low (0.26%). Patients diagnosed without chest imaging presented similarly to matched patients with cough/acute bronchitis. Most patients admitted to the hospital the same day after the UCC visit (84%) had an interim ED encounter. Pneumonia severity scores (pneumonia severity index, electronic CURB-65, and shock index) overestimated patient need for hospitalization.

Conclusions. Most UCC patients with pneumonia were successfully treated as outpatients. Opportunities to improve care include clinical decision support for diagnosing pneumonia with radiographic confirmation and development of pneumonia severity scores tailored to the UCC.

Keywords. antibiotic stewardship; community acquired pneumonia; mortality and morbidity; urgent care.

Pneumonia is a common illness treated across the spectrum of health care settings from outpatient clinics to intensive care units. While most research guiding pneumonia care was based on emergency department (ED) and hospitalized patients, a growing number of people seek care in urgent care clinics (UCCs) [1–3]. As of 2018, >112 million patients annually receive unscheduled ambulatory care in approximately 9000 UCCs across the United States, with numbers increasing [4]. Approximately 6800 patients with pneumonia are diagnosed and treated annually within 28 Intermountain Health UCCs across the state of Utah, as compared with 5000 patients in its 20 EDs.

Little is known about patient populations, processes of care, and outcomes in UCCs. An Intermountain Health audit revealed considerable variability in pneumonia care and treatment in its UCCs. Up to 40% of patients in some UCCs were diagnosed without chest imaging, which deviates from pneumonia guideline recommendations [5]. We therefore sought to better understand pneumonia care in this setting by focusing on the following questions:

- What are the characteristics of patients diagnosed with and without confirmatory imaging for pneumonia?

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- What are the differences among those patients in treatment, disposition, and 30-day mortality?
- How well do severity assessment tools—CURB-65, pneumonia severity index (PSI), and shock index—perform in UCC patients with pneumonia?

METHODS

We performed a retrospective cohort study within Intermountain Health, a vertically integrated nonprofit US health care system based in Utah. For a 24-month period from January 2019 through December 2020, we extracted electronic health record data for patients seen in its UCCs. We included all patients ≥12 years old with an *ICD-10* diagnosis of pneumonia entered by the treating UCC physician or advanced practice provider [6]. We excluded patients with a preceding encounter for pneumonia from any Intermountain Health facility within 30 days or if they were missing recorded temperature, heart rate, blood pressure, and/or oxygen saturation. Because so many patients were missing a recorded respiratory rate, we presumed it to be normal and included them in the database.

Patient Consent Statement

The Intermountain Health Institutional Review Board and the Intermountain Privacy Board approved this study (1051464).

Imaging Variation, Patient Characteristics, Treatment, and Outcomes

We separated patients diagnosed with pneumonia in the UCCs into 3 imaging categories: (1) those with confirmatory chest imaging (imaging-confirmed pneumonia), (2) those without evidence of pneumonia on chest imaging (imaging-negative pneumonia), and (3) those without chest imaging done (no imaging pneumonia). Chest imaging included posterior/anterior upright and lateral radiographs performed at the Intermountain UCCs or chest computed tomography done after the UCC encounter at an Intermountain hospital on the same day. All imaging studies were interpreted by a board-certified radiologist. Following a training period for consistency, J. H. and N. D. classified radiologist reports by *likely/possible* or *negative* for acute radiographic abnormalities consistent with pneumonia.

We gathered information on age, sex, race/ethnicity, presenting vitals, insurance status, and Charlson comorbidity score, as well as comorbidities including current smoker status, history of chronic lung disease, and diabetes. For comparison, we matched patients diagnosed with pneumonia with concurrent patients diagnosed with acute bronchitis/cough.

The primary outcomes were 30-day mortality and ED and/or inpatient hospital utilization within 7 days following UCC diagnosis of pneumonia. An additional outcome was appropriate treatment, defined as prescription of antibiotics per the guideline of the American Thoracic Society and Infectious Diseases Society of America (ATS/IDSA) and/or a planned transfer to the ED or an inpatient service. Since UCC disposition is not electronically recorded, we used time intervals between the index UCC encounter and downstream encounters (ED/hospital) to approximate planned vs unplanned transfers. Noting an inflection point in the number of downstream encounters per hour from UCC visits, we defined ≤5 hours to ED admission and ≤14 hours to inpatient as a planned transfer.

We gathered *ICD-10-CM* codes to identify secondary diagnoses for the subset of patients with downstream hospital or ED encounters. Diagnoses made in the ED or inpatient setting were the comparison standard because of expanded diagnostic capabilities as compared with Intermountain UCCs. Whereas EDs have full imaging suites and laboratory capabilities, UCCs offer limited on-site diagnostics applicable to respiratory illness: conventional chest radiography, complete blood counts, and basic metabolic panels. During the COVID-19 pandemic, point-of-care influenza and SARS-CoV-2 polymerase chain reaction tests were added.

Pneumonia Severity Assessment Tools

We evaluated the performance of commonly used pneumonia severity assessment tools in UCC patients with imaging-confirmed pneumonia. We compared an electronic version of CURB-65 (eCURB), PSI, severe community-acquired pneumonia minor criteria, and shock index (heart rate/systolic blood pressure) with the composite outcomes of 30-day mortality and 7-day hospital admission [1–3, 5]. Scores were calculated electronically. Because arterial blood gas measurements are not available in UCCs, partial pressure of arterial oxygen (at Utah's elevation of 1400 m) was calculated from SpO_2 via the Ellis equation [7]. While nursing home residency and confusion were unavailable electronically, we found these conditions rare in a chart review sample of 100 patients and thus presumed that they were not present.

Statistical Analysis

Nearest neighbor matching was used with the Mahalanobis distance measure with a control:case match of 1:3 (bronchitis/cough patients with pneumonia cases) [8]. UCC region, quarter of service date, and categorical national area deprivation index were exact matches. Sliding scale matches were age ±5 years, sex, Charlson comorbidity score ±2, race, and ethnicity. During the matching process, approximately 10% of patients were unable to be matched. At the request of reviewers, we performed a secondary sensitivity analysis with these patients included. We deemed that their exclusion did not significantly change the results (supplementary material).

Logistic regression models for imaging confirmed that pneumonia encounters were fit with the output being a composite outcome of 7-day hospital admission plus 30-day mortality. Patients <18 years old (n = 414) or missing respiratory rates (n = 547) were excluded for this part of the analysis. Missing values in PSI and eCURB were presumed normal.

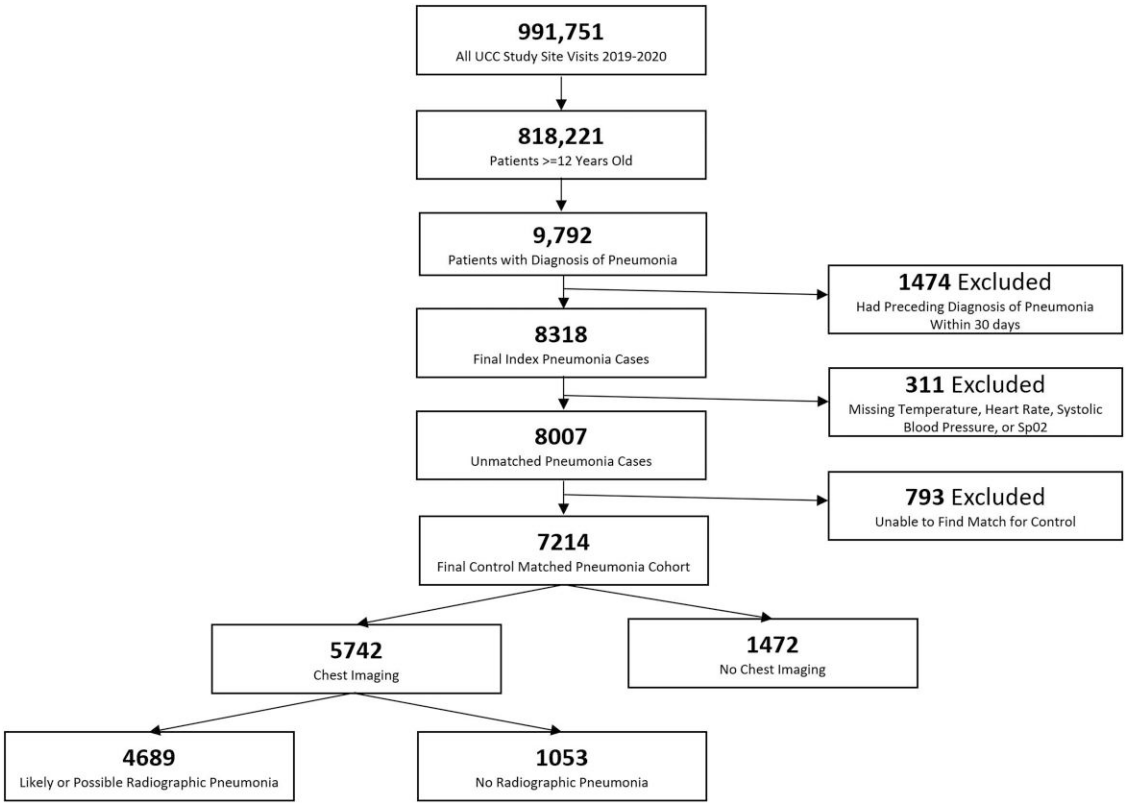

Figure 1. Patient flowchart. UCC, urgent care clinic.

The area under the curve was then calculated for PSI, eCURB, and PSI.

R version 4.0.2 was used for these analyses [9].

RESULTS

We included 7214 UCC patients diagnosed with pneumonia during the study period (Figure 1). The sample was 51.6% female with a median age of 40 years (IQR, 29–57; Table 1). Overall, 35% of UCC patients diagnosed with pneumonia did not have confirmatory imaging, either because imaging results were negative (14.6%) or no imaging was ordered (20.4%). Of all patients diagnosed with pneumonia, 50.3% had normal vital signs, half had comorbid chronic illnesses, and 6.9% were self-pay.

Patient Characteristics

Patients varied between imaging groups (Table 1). Patients with imaging-negative pneumonia were older and had higher Charlson comorbidity scores than the other pneumonia groups. Patients without imaging had lower comorbidity scores, less downstream health care utilization, and mostly normal vital signs as compared with the other 2 pneumonia groups. In the bronchitis control group, chest imaging was performed in 7095 (44%) patients, 8% of whom had possible/likely radiographic evidence of pneumonia by radiology report but were nevertheless diagnosed with cough/bronchitis by the UCC clinician. Notably, 70% of patients without imaging (pneumonia) had normal vital signs, as did 76% of the bronchitis controls vs 43% of patients with imaging-confirmed pneumonia [10, 11]. Self-pay patients were more likely to have no chest imaging vs those with third-party payers (72% vs 81%; chi-square, $P < .001$).

Disposition and Mortality Outcomes

Subsequent ED visits and hospitalizations within 7 days were infrequent in UCC patients. Of patients diagnosed with pneumonia, 553 (7.7%) had an ED visit within 7 days of the initial UCC visit, and 326 (4.5%) were admitted to the hospital, either to a ward (80.1%) or to an intensive care unit (19.9%). Most patients admitted to the hospital (84.4%) were seen in the ED prior to hospital admission after the UCC encounter. Hospital admissions and ED visits within 7 days were more common in patients with radiographically confirmed pneumonia than patients without radiographic evidence of pneumonia (6.2% vs 2.1% and 9.6% vs 6.2%, respectively; Table 2). Mortality within 30 days was low: 0.26% for those with imaging-confirmed pneumonia but <0.1% for those without imaging confirmation. A logistic regression model for the composite

Table 1. Baseline Patient Demographics and Vital Signs

Variable	Pneumonia, Median (IQR) or % (No.)			
	Imaging Confirmed (n = 4689)	Imaging Negative (n = 1053)	Imaging Not Done (n = 1472)	Matched Control (n = 15 972)
Age, y	40 (28–57)	47 (34–63)	38 (27–52)	40 (28–55)
Female	52 (2452)	52 (543)	50 (742)	56 (8893)
White Non-Hispanic	83 (3894)	84 (886)	82 (1209)	85 (13 651)
Non-White Hispanic	8 (352)	8 (86)	10 (141)	8 (1211)
Self-pay	7 (310)	4 (46)	10 (140)	6 (879)
Current smoker	6 (301)	6 (61)	5 (80)	7 (1170)
Chronic pulmonary disease	37 (1735)	48 (501)	36 (536)	40 (6313)
Asthma	13 (626)	19 (198)	14 (210)	13 (2149)
Chronic heart disease	11 (534)	18 (190)	9 (131)	10 (1588)
Dementia	0 (21)	1 (12)	0 (4)	0 (72)
Diabetes	10 (461)	16 (166)	8 (124)	9 (1434)
Liver disease	7 (325)	13 (136)	7 (101)	8 (1235)
Kidney disease	4 (177)	6 (58)	3 (38)	3 (467)
Cancer	5 (215)	7 (77)	3 (51)	4 (635)
Comorbidity				
Other	6 (285)	9 (96)	6 (89)	6 (961)
Any	48 (2256)	62 (653)	47 (692)	50 (8031)
No	52 (2433)	38 (400)	53 (780)	50 (7941)
Charlson score	1.00 (0.00–2.00)	1.00 (1.00–4.00)	1.00 (0.00–2.00)	1.00 (0.00–2.00)
Vital signs				
Temperature ≥37.8 °C	31 (1453)	22 (235)	13 (192)	7 (1082)
Respiratory rate ≥24	10 (480)	8 (85)	4 (53)	3 (547)
Missing respiratory rate	12 (547)	17 (181)	35 (521)	15 (2381)
Heart rate ≥100	42 (1959)	30 (315)	22 (329)	18 (2915)
SpO_2 <90%	4 (200)	2 (24)	1 (13)	0 (74)
Sum of vital signs (above)				
Normal	43 (2002)	57 (597)	70 (1033)	76 (12 176)
Any 1 abnormal	32 (1513)	27 (283)	21 (302)	19 (3045)
Any 2 abnormal	21 (965)	14 (145)	9 (126)	4 (684)
Any 3 abnormal	4 (187)	2 (26)	1 (11)	0 (63)
All 4 abnormal	0 (22)	0 (2)	0 (0)	0 (4)
30-d observed mortality	0.26 (12)	0.09 (1)	0.07 (1)	0.06 (10)

outcome of 30-day all-cause mortality and/or hospital admission yielded an area under the curve of 0.84 (Table 3).

Treatment

Most patients diagnosed with pneumonia (97.2%) were prescribed antibiotics and/or had a planned ED/inpatient admission, as opposed to 24.6% in the acute bronchitis group (Table 2). Most patients admitted to the hospital the same day after the UCC visit (84%) had an interim ED encounter (ie, they were not direct admitted). Most patients with pneumonia (93.2%) received antibiotics consistent with ATS/IDSA 2019 pneumonia guideline recommendations (amoxicillin, amoxicillin/clavulanate, doxycycline, or cefdinir) [5]. A parenteral antibiotic (mostly ceftriaxone) was administered in the UCC for 28.7% of patients with imaging-confirmed pneumonia.

Subsequent Diagnoses

Of UCC patients initially diagnosed with pneumonia who had a subsequent ED visit and/or hospital admission, 398 (80%) of those with imaging-confirmed pneumonia had a pneumonia diagnosis confirmed at that later visit. In patients with imaging-negative pneumonia, a subsequent diagnosis of pneumonia was present in only 16 (24%). For those with no imaging done, 16 (37%) were diagnosed with pneumonia. Therefore, we conservatively estimate that UCCs overdiagnose pneumonia by 30%. Notably, 6 (9%) patients with imaging-negative pneumonia were secondarily diagnosed with pulmonary embolism, as compared with 18 (4%) of those with imaging-confirmed pneumonia and 1 (2%) with no imaging. Seven (2%) patients with bronchitis/cough also had pulmonary emboli on later visits.

Pneumonia Severity Assessment Tools

The PSI and shock index were significantly associated with the composite outcome of mortality and/or 7-day hospital admission on logistic regression, but the area under the receiver operating characteristic curve was only 0.73 for eCURB, 0.73 for PSI, and 0.56 for shock index. Table 4 shows that most UCC patients who would be recommended for hospital admission with

Table 2. Pneumonia Treatment and Downstream Health Care Utilization

Variable	Pneumonia, % (No.) or Median (IQR)			
	Chest Radiograph Confirmed (n = 4689)	Chest Radiograph Negative (n = 1053)	Chest Radiograph Not Done (n = 1472)	Matched Control (n = 15 972)
Antibiotic prescription	93 (4340)	92 (966)	93 (1374)	24 (3860)
IV/IM antibiotics	29 (1345)	11 (117)	9 (132)	0 (66)
IV fluid administered	3 (158)	0 (3)	0 (5)	0 (18)
ED visit <7 d	10 (448)	6 (65)	3 (40)	2 (320)
ED visit ≤5 h	4 (208)	3 (32)	0 (1)	0 (62)
Hospital admission <7 d	6 (293)	2 (22)	1 (11)	1 (81)
Hospital length of stay, d	2.90 (1.90–4.90)	2.40 (1.83–3.05)	2.40 (2.25–3.15)	3.00 (1.80–4.20)
ICU admission	1 (59)	0 (3)	0 (3)	0 (9)

Abbreviations: ED, emergency department; ICU, intensive care unit; IM, intramuscular; IV, intravenous.

Table 3. Multiple Logistic Regression for Composite Outcome of 30-Day Mortality and/or Hospital Admission for Imaging-Confirmed Pneumonia

Variable	Odds Ratio (95% CI)	*P* Value
Intercept	0.00 (.00–.00)	<.001
Age	1.01 (.99–1.02)	.463
Female	0.83 (.62–1.11)	.213
eCURB, %	1.06 (.98–1.16)	.141
SCAP minor criteria [5]	1.95 (1.44–2.65)	<.001[a]
Multilobar infiltrates	1.46 (.97–2.21)	.073
Shock index × 100[b]	1.03 (1.02–1.04)	<.001[c]
SpO_2	0.84 (.81–.88)	<.001[d]
PSI	1.64 (1.33–2.02)	<.001[e]

Only imaging-confirmed pneumonia cases with exclusion of patients <18 years old (n = 414), since the scores were not developed for patients aged <18 years. Patients missing respiratory rates (n = 547) were also excluded since eCURB cannot be determined. We also performed LASSO logistic regression over concern for colinearity, but the model estimates were almost identical; thus, results are not provided.

Abbreviations: eCURB, an electronic version of CURB-65 that utilizes continuous and weighted elements; PSI, pneumonia severity index; SCAP, severe community-acquired pneumonia.

[a]As SCAP increases by 1 point, the odds of being admitted to the hospital or dying increase by 95% ($P < .001$).

[b]Since shock index ranges from 0.27 to 1.75, a 1-unit increase spans almost the entire range of values. We therefore multiplied shock index by 100.

[c]As shock index increases by 0.01, the odds of being admitted to the hospital or dying increase by 3% ($P < .001$).

[d]As SpO_2 increases by 1%, the odds of being admitted to the hospital or dying decrease by 16% ($P < .001$).

[e]As PSI increases by 1 class, the odds of being admitted to the hospital or dying increase by 64% ($P < .001$).

Table 4. Severity of Illness Scores: Imaging-Confirmed Pneumonia

	Hospital Admission <7 d or 30-d Mortality, % (No.)[a]	
	No (n = 3466)	Yes (n = 262)
PSI[b]		
1 (n = 1955)	97.3 (1903)	2.7 (52)
2 (n = 1143)	92.4 (1056)	7.6 (87)
3 (n = 347)	84.7 (294)	15.3 (53)
4 (n = 242)	78.1 (189)	22.9 (53)
5 (n = 41)	58.5 (24)	41.5 (17)
eCURB ≥5% (n = 63)[c]	50.0 (33)	47.6 (30)
Shock index ≥1 (n = 195)[d]	82.6 (161)	17.4 (34)

Abbreviations: eCURB, an electronic version of CURB-65 that utilizes continuous and weighted elements; PSI, pneumonia severity index.

[a]Imaging-confirmed pneumonia cases with exclusion of patients <18 years old (n = 414), since the scores were not developed for patients aged <18 years, and patients missing respiratory rates (n = 547).

[b]Hospital admission is advised with PSI ≥3.

[c]eCURB ≥5% is comparable to a CURB65 score ≥2 where hospital admission is advised.

[d]Shock index = heart rate divided by systolic blood pressure. Shock index values ≥1 have been widely associated with mortality and morbidity.

the PSI, eCURB, or shock index were successfully treated at home.

DISCUSSION

Our study demonstrates that many patients evaluated for pneumonia in UCCs experience care that varies from diagnosis and treatment guidelines. Patients are much younger than ED or hospital pneumonia cohorts, have lower 30-day mortality, and are mostly treated as outpatients. Many opportunities are evident for improving care and patient outcomes in this underexplored population.

Multiple reasons contribute to the 35% of patients diagnosed with pneumonia without imaging confirmation. Patients with negative imaging results were older and had more comorbid illnesses than other groups, suggesting that risk of adverse outcomes may influence medical decision making. Radiologist interpretations are often delayed during busy times, as well as evenings, weekends, and holidays. This requires the UCC provider to diagnose pneumonia based on the interpretation of imaging findings, which might differ from the later radiologist report. For patients without imaging, payer status and concerns over costs of imaging may discourage the ordering of chest imaging. Other factors include staffing shortages, equipment malfunctions, and local practice patterns.

UCCs' pneumonia populations are different from ED patients and may require different tools for guiding care and measuring severity of illness. As compared with previously

published data of Utah ED patients with pneumonia, UCC patients with radiographically confirmed pneumonia had comorbid conditions less often (48% vs 68%) and were much younger (40 vs 67 years), although they had similar gender, ethnic, and racial characteristics [6]. The younger and healthier demographic in UCCs may explain our finding that established pneumonia severity tools overestimate mortality risk and need for hospitalization. Abnormal vitals are a key feature for deciding to obtain chest imaging, but 43% of UCC patients with imaging-confirmed pneumonia presented with normal vital signs [11]. These differences in UCC patients with pneumonia warrant further study and consideration of modifications to severity-of-illness tools.

While prescribing practices were well aligned with ATS/IDSA recommendations, diagnostic accuracy needs improvement. The pneumonia cohort without imaging is similar to the matched group with acute bronchitis in vital signs and outcomes. Confirmatory diagnoses of pneumonia were uncommon among patients without supportive imaging (negative or no imaging) who later required ED or inpatient evaluation. While many factors contribute to this variability, one possibility is the need for better provider diagnostic and treatment support in UCCs. A care process model for community-acquired pneumonia has existed in paper format for 25 years at Intermountain Health, but no clinical decision support is incorporated into the electronic health record workflow.

Finally, pneumonia care in UCCs provides an additional opportunity for ongoing antibiotic stewardship. Due partly to prior antibiotic stewardship campaigns, we observed high ATS/IDSA antibiotic compliance in patients diagnosed with pneumonia and low antibiotic prescribing rates for patients with bronchitis [12]. Our estimate of 30% overdiagnosis suggests thousands of unnecessary antibiotic prescriptions annually [13]. Code shifting may have also been present (ie, choosing one diagnosis over another to comply with quality improvement efforts).

Limitations

Several limitations exist. Patients with pneumonia who had missing vital signs other than respiratory rate were excluded (3.7%), and data important for pneumonia care are not coded, including mental status, lung auscultation findings, and nursing home residence. Only 15% of patients with imaging-confirmed pneumonia have basic blood tests. These characteristics reflect the low-acuity, lower-cost, and high-volume nature of UCCs.

Second, subsequent ED or hospital admissions after the UCC visit were identified only in Intermountain Health hospitals. Patients with preferences for or contracted health plans requiring admission in a different health system result in missing downstream health care information. An audit within this data set indicated that 14.5% of transferred patients were sent to non-Intermountain hospital EDs.

Third, part of the study period included the COVID-19 pandemic. Although only 2% of our study population tested positive for SARS-CoV-2, no testing was available early in the pandemic. Just 6% of our study population had any COVID-19 testing at all. UCC pneumonia cases dropped in 2020 by 44.5% (3839 cases in 2020 vs 6927 cases in 2019), perhaps due to indirect effects of masking and social distancing and fewer patients seeking treatment for mild to moderate symptoms.

Fourth, 8% of patients coded as having bronchitis/cough with suggestive chest imaging had possible or likely radiographic pneumonia. Some may have had their diagnosis changed to pneumonia when the radiology report later became available, but the *ICD-10* visit code was not updated. For others, the bedside clinician likely diagnosed acute bronchitis/cough rather than pneumonia using clinical judgment.

Interventions

We have identified opportunities to improve pneumonia diagnosis and treatment in UCCs. Principal challenges included missing respiratory rate documentation, diagnosis of pneumonia without confirmatory chest imaging, delays in radiologist interpretations, lack of validated severity scoring tools for UCCs, and unnecessary ED visits between UCC and hospital admission. To address these, we are implementing the following interventions:

- To overcome delays in radiologist interpretation, we are deploying an artificial intelligence model to preliminarily identify radiographic pneumonia findings as soon as images are uploaded.
- We created an alert within the electronic medical record to discourage clinicians from entering a diagnosis of pneumonia without radiographic confirmation.
- We have deployed an electronic health record–integrated pneumonia clinical decision support tool called ePneumonia in a cluster of 5 UCC clinics as part of a pilot trial (ClinicalTrials.gov NCT04606849). ePneumonia provides real-time electronic guidance for diagnosis, disposition/site of care, and treatment, and it facilitates direct hospital admissions for patients meeting hospitalization criteria for hospital ward admission [6].

CONCLUSION

Community-acquired pneumonia is frequently diagnosed and treated in UCCs, but care varies from diagnosis and treatment guidelines. Pneumonia severity tools perform less well in UCCs. We have described underutilization in chest imaging for diagnosing pneumonia in this population. Patients diagnosed without confirmatory imaging likely receive unnecessary antibiotics, and some have a serious alternate diagnosis such as pulmonary embolism. We propose interventions to improve care of UCC patients suspected of pneumonia.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. J. H. H. and N. C. D. had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: J. H. H., N. C. D. Acquisition, analysis, or interpretation of data: all authors. Drafting of the manuscript: J. H. H., T. S., N. C. D. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: A. M. B., J. R. E. Obtained funding: N. C. D. Administrative, technical, or material support: None. Supervision: N. C. D.

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Potential conflicts of interest. All authors: No reported conflicts.

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