Published in final edited form as:

J Nephrol. 2013 ; 26(6): 1128–1135. doi:10.5301/jn.5000296.

Pneumonia in hemodialysis patients: a challenging diagnosis in the emergency room

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Abstract

Background—Diagnosing pneumonia in hemodialysis patients is challenging. We hypothesized that pulmonary edema, which occurs commonly in hemodialysis patients, may frequently be misdiagnosed as pneumonia.

Methods—We retrospectively reviewed the records of 105 hemodialysis patients admitted with the diagnosis of pneumonia. Two experienced radiologists masked to the clinical course and subsequent imaging, independently interpreted the admission chest radiographs. In 68 of the patients, 2 internists independently reviewed the hospitalization records to diagnose pneumonia and pulmonary edema. The level of agreement among the radiologists was assessed using the kappa test. Using the clinical diagnoses, chest radiograph attributes were calculated. Logistic regression was performed to identify clinical and laboratory markers associated with pneumonia and pulmonary edema.

Results—The radiologist showed slight agreement on pneumonia ($\kappa = 0.32$) and pulmonary edema ($\kappa = 0.28$). Using clinical consensus, pneumonia was diagnosed in only 21% (14/68) of patients. Chest radiograph attributes for diagnosing pneumonia included: sensitivity 50%, specificity 58%, positive predictive value 25% and negative predictive value 81%. Pneumonia was associated with presenting temperature (odds ratio [OR] = 2.01; 95% CI, 1.03–3.93). Pulmonary edema was associated with shortness of breath (SOB) at admission (OR = 4.83; 95% CI, 1.25–18.6), presenting temperature (OR = 0.44; 95% CI, 0.21–0.92) and volume removed during hemodialysis (OR = 1.96; 95% CI, 1.16–3.31).

Conclusions—The admission chest radiograph has significant limitations when used to diagnose pneumonia in hemodialysis patients. A high presenting temperature supports the

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Conflict of interest: None.

Parts of this study were presented at the Nephrology Young Investigators Forum, May 2012, Washington DC, and in abstract form at the National Kidney Foundation's spring clinical meeting, May 2012, Washington DC.

Bin Zhang, PhD, assistant professor in the Division of Biostatistics and Epidemiology at Cincinnati Children's Hospital Medical Center, provided statistical assistance.

diagnosis of pneumonia, while a low presenting temperature, SOB and large volume ultra-filtration favor the diagnosis of pulmonary edema.

Keywords

Chest; Hemodialysis; Infection; Infiltrate; Pneumonia; Radiograph; Sensitivity; Pulmonary edema

Introduction

Pneumonia is an infection of the lung that typically causes purulent sputum, fever, hypoxemia and an infiltrate on lung imaging. It has been subdivided into categories to guide clinical management: community-acquired pneumonia (CAP), health care-associated pneumonia (HCAP), hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP). In-center hemodialysis patients who contract pneumonia outside the hospital fall into guideline definitions of HCAP (1); yet, except for an increased risk of methicillin-resistant *Staphylococcus aureus* infection, hemodialysis patients with pneumonia can be treated as having CAP (2). Pneumonia is diagnosed much more commonly in hemodialysis patients than in the general population. Whereas the incidence of CAP in the United States in adults 65 years of age is 2.5/100 person-years (3), it is more than 10-fold higher in hemodialysis patients, at 29/100 person-years by Medicare claims data (4). Pneumonia is diagnosed in 1 in 5 patients in the first year of starting hemodialysis (4). Although the higher rate of pneumonia diagnosis in hemo-dialysis patients may reflect an increased risk of infection, there may also be a component of overdiagnosis.

Diagnosing pneumonia incorporates 2 imperfect testing modalities – namely, clinical judgment and the chest radiograph (CXR). Studies have highlighted the limitations of both clinical findings and the CXR for diagnosing pneumonia in the general population (5–11), but the diagnosis of pneumonia has never been evaluated systematically in the dialysis population. Dialysis patients are specifically susceptible to volume overload and pulmonary edema, which may complicate the diagnosis of pneumonia. Pulmonary edema can mimic pneumonia, both in terms of presenting with an abnormal CXR, as well as producing a similar clinical presentation. The present study had 2 major goals: (i) to evaluate the accuracy and reliability of the CXR in diagnosing pneumonia in hemodialysis patients and (ii) to identify clinical markers associated with the diagnosis of pneumonia in hemodialysis patients.

Subjects and methods

Study population

Hemodialysis patients admitted to the University Hospital at the University of Alabama at Birmingham (UAB) (an urban, 1,000-bed, academic medical center) were identified retrospectively by *International Classification of Diseases*, Ninth Revision, Clinical Modification codes for pneumonia (480.0–487.0) and the administration of antibiotics in the emergency department, available through hospital information systems. The UAB institutional review board approved the study. Of the 122 patients admitted during calendar year 2010, a total of 17 patients were excluded from initial analysis: 15 requiring continuous

renal replacement therapy and 2 lacking an admission CXR. The remaining 105 admission chest radiographs were analyzed. A further 37 patients had missing dialysis records, leaving a consensus clinical diagnosis of pneumonia and/or pulmonary edema to be established for a total of 68 patients.

Study design

The study was divided into 2 parts. The first part assessed the interrater reliability of the CXR in diagnosing pneumonia and pulmonary edema in hemodialysis patients, and the second part evaluated the association of clinical and laboratory markers with the diagnosis of pneumonia and pulmonary edema in hemodialysis patients. For the first portion, 2 experienced radiologists (reading an average of 3,000 and 17,000 CXRs per year, respectively) independently interpreted the admission CXRs for the presence of pneumonia and/or pulmonary edema. Both radiologists received only patient identifiers, date of the CXR and type of CXR. They were masked to the patients' clinical course and subsequent imaging studies and encouraged to read each radiograph as a typical admission CXR, with the ability to compare with prior imaging if available. The radiologists were aware that the patients were hemodialysis patients. They were asked to score the presence of pneumonia and pulmonary edema by answering the following question: "After reviewing the CXR, do you feel the patient had pneumonia, pulmonary edema, both or neither?"

Two internal medicine-trained physicians independently determined the presence of pneumonia and pulmonary edema after reviewing the entire medical record, which included the hospital course, response to hemodialysis, hemodialysis treatment information, subsequent radiographic imaging including CXRs and computed tomography (CT) imaging of the chest, microbiology data (blood, sputum and bronchoscopy culture), discharge summary and future hospitalizations or clinic visits. Clinician disagreement was adjudicated by a face-to-face meeting to reach consensus diagnoses of pneumonia and pulmonary edema for each patient. Adjudication by consensus clinician agreement has been used previously to diagnose infections (including pneumonia) in a large study of hemodialysis patients (12). Clinical diagnoses of pneumonia and pulmonary edema were reached by consensus agreement in 96% (65 of 68 patients) and 99% (67 out of 68 patients), respectively. For the purpose of our analysis, the adjudicated diagnosis was considered to be the true clinical diagnosis for each patient.

Clinical data were collected for the second portion of the study. Each patient's presenting signs and symptoms and medical history were recorded from admission documentation including the emergency room note and the resident history and physical examination. Selected laboratory data at presentation, microbiology data throughout the hospitalization and hemodialysis orders and nursing flow sheets were also collected. The validated prediction score for pneumonia severity in the general population, the pneumonia severity index (PSI), was calculated for each patient (13).

Radiographic diagnostic criteria

The admission chest radiograph was categorized into 4 groups (pulmonary edema, pneumonia, neither or both) using the following criteria: Pulmonary edema required the

presence of symmetric interstitial or airspace opacities, Kerley lines, cardiomegaly and/or a pleural effusion. Pneumonia was characterized by asymmetric or focal airspace density, air bronchograms and the absence of lung volume loss. The category of *neither* contained normal chest radiographs as well as those with mild vascular redistribution (especially on single anteroposterior views, i.e., portable films), an opacity associated with lung volume loss typical of atelectasis, and only pleural effusion(s) or cardiomegaly without interstitial thickening. Radiographs categorized as supporting diagnoses for both pneumonia and pulmonary edema consisted of asymmetric, mixed interstitial and airspace opacities.

Statistical analysis

Kappa statistics, a measure of interrater reliability that adjusts for random agreement, were used to assess the statistical significance of agreement between the 2 radiologists. A kappa coefficient greater than 0.75 indicates excellent agreement, a kappa of 0.4 to 0.75 indicates fair to good agreement and a kappa less than 0.4 indicates poor agreement beyond chance (14). Using adjudicated diagnoses of pneumonia and pulmonary edema as the true clinical diagnosis, 2×2 tables were created for each radiologist, which allowed for the calculation of CXR attributes (sensitivity, specificity, negative predictive value and positive predictive value) in the study population.

Clinical data extracted from the medical records were analyzed by multivariable logistic regression to identify covariates strongly correlated with the diagnosis of pneumonia or pulmonary edema. Odds ratios (OR) and their associated 95% confidence intervals (95% CI) were calculated, with a p value <0.05 considered to be statistically significant. All statistical calculations were performed with SAS software (version 9.3; SAS Institute, Cary, NC, USA).

Results

Patient characteristics

Table I shows the patient characteristics for the 68 study patients who underwent clinical adjudication. The mean patient age was 56 years (range 21 to 85 years), 44% were female, and about three fourths were black. The majority of patients (66%) complained of shortness of breath, while only 31% reported a productive cough. Overall, 54 of the patients (79%) had at least 1 comorbid condition. Fever, defined as an admission temperature $\geq 38^{\circ}\text{C}$, was present in 11 patients (16%). The majority of patients were at low risk for mortality as predicted by the PSI. A PSI score ≤ 90 points is considered a low risk for death, while scoring more than 130 points predicts the highest risk of death (13). The mean PSI in this study was 53.8 points (range 0 to 140 points).

Interrater agreement

The 2 study radiologists agreed on the presence or absence of pneumonia in 70 out of the 105 CXRs (Tab. II). Kappa coefficients for agreement between the 2 radiologists were 0.32 and 0.28 for pneumonia and pulmonary edema, respectively, which showed slight agreement. Of the 105 CXRs, 75 were single anteroposterior views (portable films), while the remaining 30 CXRs were posteroanterior and lateral views. Radiologist agreement for

pneumonia was similar regardless of the CXR type (65.3% with portable and 70% with posteroanterior and lateral).

Chest radiograph attributes

Clinical adjudication established the diagnosis of pneumonia in 14 out of 65 patients and pulmonary edema in 37 out of 67 patients. Diagnoses were not exclusive, as 2 patients were diagnosed with both pneumonia and pulmonary edema. Using these diagnoses, the CXR had a sensitivity for diagnosing pneumonia in hemodialysis patients of $50\% \pm 27\%$, a specificity of $58\% \pm 14\%$, a positive predictive value of $25\% \pm 14\%$, and a negative predictive value of $81\% \pm 14\%$ (Tab. III). The CXR attributes for pulmonary edema varied between the 2 radiologists (Tab. IV).

Identifying clinical markers of pneumonia and pulmonary edema

Previously reported clinical markers associated with the diagnosis of pneumonia in the general population (fever, productive cough, hypoxia and pulmonary crackles) in addition to laboratory data (i.e., white blood cell count) were tested for association in our hemodialysis population using logistic regression analysis. Temperature at presentation to the emergency room was significantly associated with the diagnosis of pneumonia (OR = 2.01; 95% CI, 1.03–3.93) (Fig. 1). Significant associations between covariates and the diagnosis of pulmonary edema were discovered in 3 clinical factors: shortness of breath at admission (OR = 4.83, 95% CI, 1.25–18.6), presenting temperature (OR = 0.44; 95% CI, 0.21–0.92) and volume removed during hemodialysis (OR = 1.96; 95% CI, 1.16–3.31) (Fig. 2).

Discussion

The diagnosis of pneumonia in the general population is not clear cut. It involves combining the clinical interpretation of signs, symptoms, laboratory and microbiological data with a pulmonary infiltrate on chest imaging (2). Both clinical judgment and radiographic findings have known limitations in the general population. However, the value of the CXR for diagnosing pneumonia has not been reported in hemodialysis patients. We hypothesized that the higher prevalence of pulmonary edema in hemodialysis patients would magnify the limitations of the CXR and make pneumonia more difficult to diagnose. For example, asymmetric opacities in the lower lung zone of the chest radiograph may represent pneumonia or pleural effusion (Fig. 3). We first evaluated the reliability and accuracy of the CXR for diagnosing pneumonia in our hemodialysis population. Interrater agreement for identifying a pulmonary infiltrate on CXR is not high in the general population, ranging from slight ($\kappa = 0.27$) to fair ($\kappa = 0.37$) (5, 6). In the hemodialysis population we found a similar interrater agreement ($\kappa = 0.32$). The sensitivity and specificity of the CXR for diagnosing pneumonia in the general population is reported to be 60% and 29%, respectively, when compared with protected bronchial brush cultures in patients suspected of having ventilator-associated pneumonia (5), and 32%–65% and 74%–93%, respectively, when compared with CT chest imaging in bedridden patients suspected of having pneumonia (7). In our hemodialysis population, we found similar results (sensitivity of 50% and a specificity of 57%–59%) when clinical adjudication was used to establish the diagnosis of pneumonia.

We then sought to identify clinical markers associated with the diagnosis of pneumonia in the hemodialysis population. Similar to the CXR, clinical judgment lacks sensitivity and specificity for diagnosing pneumonia in the general population. A study by Lieberman et al reported clinical judgment to have a sensitivity of 74% (40%–90%), a specificity of 84% (78%–88%), a negative predictive value of 97% (94%–99%) and a positive predictive value of 27% (16%–42%) in ambulatory, febrile adults when compared with serial CXRs interpreted by 2 senior radiologists (8). The physical examination was a poor predictor of pneumonia in adult patients (9, 10), and a systemic review by Metlay et al failed to identify any clinical findings that could confirm the diagnosis of pneumonia (11). In our hemodialysis population, we were only able to identify presenting temperature as a clinical marker associated with the diagnosis of pneumonia. These observations highlight the conclusion that pneumonia is a complex clinical diagnosis, which requires careful integrated review of all of the available clinical and radiologic information (12).

What are the clinical implications from the results of this study? Our findings support the hypothesis that pneumonia is overdiagnosed in hemodialysis patients. Hemodialysis patients with pulmonary edema may be more likely to be treated for pneumonia, increasing antibiotic exposure. In our sample of hemodialysis patients with an admission diagnosis of pneumonia, only 21% were felt to have pneumonia after clinical adjudication, yet 72% completed a full course of antibiotics for pneumonia treatment. Our findings suggest that once a tentative diagnosis of pneumonia has been made, antibiotics are usually continued even when the clinical evidence does not favor the diagnosis of pneumonia.

With only slight radiologist agreement in interpreting the admission CXR in addition to a low sensitivity and specificity to diagnose pneumonia, one may be tempted to avoid getting an admission CXR in low-risk hemodialysis patients suspected of having pneumonia, perhaps favoring CT imaging of the chest. However, we are unaware of any studies linking the more costly CT chest imaging to improved outcomes in hemodialysis patients suspected of having pneumonia. Guidelines recommend obtaining a CXR (preferably pos-teroanterior and lateral) in every patient suspected of having pneumonia (2). A potentially clinically useful interpretation of our results is that identifying the limitations of the CXR in diagnosing pneumonia in hemodialysis patients enhances clinician judgment. For example, interrater agreement has been reported to be higher in the absence of an infiltrate (94% with kappa of 0.53) (15). Our study showed the CXR to have a high negative predictive value (81%) when considering the diagnosis of pneumonia. Therefore, the absence of an infiltrate on CXR may be a useful tool for excluding pneumonia in hemodialysis patients.

The multivariable logistic regression analysis revealed another clinical implication of this study. A high presenting temperature was associated with the diagnosis of pneumonia, while lower temperatures and shortness of breath correlated with pulmonary edema in our sample of hemodialysis patients. If a patient presents with shortness of breath, is afebrile, and symptomatically improves after aggressive fluid removal on dialysis; then the patient is likely to have pulmonary edema. In this setting, unless the clinical suspicion for pneumonia is high, the admission symptoms may be explained by pulmonary edema, and antibiotics could be stopped regardless of the presence of an infiltrate on admission CXR. An important exception to discontinuing antibiotic therapy may be seen in patients with a history of

chronic obstructive pulmonary disease (COPD), where antibiotic therapy is not contingent upon a diagnosis of pneumonia. In addition, it is possible that pneumonia can worsen or lead to pulmonary edema, especially in patients with heart failure. In this case, symptomatic improvement after dialysis could mask an underlying pneumonia, although, in this study, combined diagnoses of pneumonia and pulmonary edema were rare (2 out of 68 patients).

Our study has some limitations. First, it represents the results from a single clinical dialysis center, and may not generalize to all dialysis centers. Second, most of the patients had a relatively low pneumonia severity index and the results may differ in patients with higher clinical severity. Third, the study was restricted to dialysis outpatients presenting to the emergency room, and the findings may not extrapolate to patients who develop findings suspicious for pneumonia during their hospitalization. Fourth, there is no established gold standard for diagnosing pneumonia in ambulatory patients. Studies in the general population have used CT imaging or protected bronchial cultures to diagnose pneumonia, yet these modalities carry their own limitations. Ultimately, the diagnosis of pneumonia remains clinical, and clinician judgment is the current standard of care in patients with low-risk pneumonia (12). Furthermore, radiologist agreement (interrater reliability) is independent of clinically established diagnoses. Fifth, an ascertainment or sampling bias was introduced through the retrospective design. Study patients were selected by an admission diagnosis of pneumonia, which was partially established by the admission CXR. Patients who may have been ruled out for pneumonia by the admission CXR were missed. In addition, clinical diagnoses of pneumonia and pulmonary edema were not performed in 54 out of the 122 eligible patients due to missing dialysis records or their requirement for continuous renal replacement therapy. Sixth, a type 2 statistical error may be present in the logistic regression analysis given the sample sizes of 65 and 67 patients. Seventh, the study radiologists interpreted only the admission CXRs; interpretation of serial CXRs, especially those obtained after a hemodialysis treatment, may improve diagnostic accuracy and reliability. However, many patients did not receive a follow-up CXR if they improved clinically. Also, the subset analysis of radiologist agreement by type of CXR (portable vs. posteroanterior and lateral) did not show a change in agreement (65.3% vs. 70%); yet posteroanterior and lateral CXRs may improve both the specificity (less atelectasis in the lung above the diaphragm and increased visualization of effusions) and sensitivity (improved visualization of the lower lungs) of the CXR (16). Finally, the small number of upper lobe opacities (present in 4 of the 105 CXRs studied), limited analysis of upper lobe disease, which may be more specific for pneumonia in this population.

In summary, the limitations of the admission CXR, when used as a diagnostic tool for pneumonia, are magnified in the hemodialysis population where pulmonary edema is more prevalent. The major value of the CXR may be to decrease the probability of pneumonia when reported as negative for pneumonia. The CXR limitations in combination with a lack of clear markers to guide clinical judgment make diagnosing pneumonia in hemodialysis patients challenging. Therefore, the diagnosis of pneumonia may be frequently incorrect in hemodialysis patients, resulting in prolonged unnecessary antibiotic exposure.

Acknowledgments

Financial support: National Institutes of Health Grant T32 HL007457 (to EJ).

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Fig. 1.

Forest plot showing factors associated with pneumonia in hemodialysis patients. Results calculated by multivariable logistic regression using clinical adjudication for the diagnosis of pneumonia. COPD = history of chronic obstructive pulmonary disease; BMI = body mass index (kg/m^2); leukocytosis = admission white blood count $>11 \times 10^3$ cells/ μL ; Temp = presenting temperature (per 1°C); Sodium = presenting serum sodium (mEq/L); OR = odds ratio; CI = confidence interval. ¹Age per 10 years.

Fig. 2.

Forest plot showing factors associated with pulmonary edema in hemodialysis patients. Results calculated by multivariable logistic regression using clinical adjudication for the diagnosis of pulmonary edema. SOB = shortness of breath on admission; Temp = presenting temperature (per 1°C); Obesity = body mass index ≥ 30 (kg/m²); Ultrafiltrate = hemodialysis ultrafiltrate volume (L); OR = odds ratio; CI = confidence interval. ¹Pleural effusion defined as a pleural effusion identified on admission chest radiograph.

Fig. 3. Single anteroposterior, portable chest radiograph showing pulmonary edema with asymmetric radio opacity in the right lower lung zone that may represent pneumonia or pleural effusion.

TABLE I

PATIENT CHARACTERISTICS FOR THE STUDY POPULATION^{†*}

Patient characteristic	Frequency
Age, mean years $\pm$ SD	56 $\pm$ 14.8
African American	52 (76)
Female	30 (44)
Symptoms	
Shortness of breath	45 (66)
Cough	21 (31)
Fever	11 (16)
Comorbid conditions	
Smoking history	33 (49)
Heart failure history	19 (28)
Altered mental status	17 (25)
Nursing home resident	8 (12)
Cancer history	7 (10)
Liver disease	7 (10)
Stroke history	6 (9)
COPD	12 (18)
Obesity	20 (29)
Pneumonia severity index, mean points $\pm$ SD	53.8 $\pm$ 29.6
Admission vital signs, mean $\pm$ SD	
Temperature ($^{\circ}$ C)	37.1 $\pm$ 1.0
Respiratory rate (breaths/min)	23 $\pm$ 6.9
Systolic blood pressure (mm Hg)	149 $\pm$ 44
Diastolic blood pressure (mm Hg)	81 $\pm$ 26
Heart rate (beats/min)	102 $\pm$ 25
Selected laboratory variables, mean $\pm$ SD	
Serum sodium (mEq/L)	136 $\pm$ 4.0
Hematocrit (%)	33 $\pm$ 6.9
Blood urea nitrogen (mg/dL)	47 $\pm$ 32
White blood cell count ($10^3/\mu$ L)	11 $\pm$ 5.9
Hemodialysis variable, mean $\pm$ SD	
Ultrafiltration (L) [†]	2 $\pm$ 1.4

Values are number (%), unless specified otherwise. COPD = chronic obstructive pulmonary disease.

* Hemodialysis patients admitted from the emergency department, suspected of having pneumonia.

[†] Ultrafiltration is the total volume of fluid removed during the first dialysis session after hospitalization.

TABLE II
RADIOLOGIST DETECTION OF PNEUMONIA ON ADMISSION CHEST RADIOGRAPH IN THE STUDY POPULATION*

		Radiologist 2			Kappa test for agreement†
		No	Yes	Total	
Radiologist 1	No	42	19	61	0.32 (0.14, 0.50)
	Yes	16	28	44	
	Total	58	47	105	

* Hemodialysis patients admitted from the emergency department, suspected of having pneumonia.

† Simple kappa coefficient with 95% confidence interval.

TABLE III**CHEST RADIOGRAPH: ATTRIBUTES OF THE TEST FOR PNEUMONIA IN THE STUDY POPULATION***

	Radiologist 1		Radiologist 2	
		95% CI		95% CI
Sensitivity (%)	50	23–77	50	23–77
Specificity (%)	57	42–71	59	44–72
PPV (%)	24	10–38	25	11–39
NPV (%)	81	64–92	81	65–92

CI = confidence interval; PPV = positive predictive value; NPV = negative predictive value.

* Results calculated using clinical adjudication for the diagnosis of pneumonia in hemodialysis patients admitted from the emergency department, suspected of having pneumonia.

TABLE IV

CHEST RADIOGRAPH: ATTRIBUTES OF THE TEST FOR PULMONARY EDEMA IN THE STUDY POPULATION*

	Radiologist 1		Radiologist 2	
		95% CI		95% CI
Sensitivity (%)	62	45–79	92	78–100
Specificity (%)	80	61–92	33	17–53
PPV (%)	79	60–98	63	49–77
NPV (%)	63	46–78	77	46–95

CI = confidence interval; PPV = positive predictive value; NPV = negative predictive value.

* Results calculated using clinical adjudication for the diagnosis of pulmonary edema in hemodialysis patients admitted from the emergency department, suspected of having pneumonia.