The Diagnosis of Community-acquired Pneumonia
Do We Need to Take a Big Step Backward?

Good research is supposed to clear up controversy and move us forward with greater understanding. Just occasionally, however, good research does exactly the opposite.

Community-acquired pneumonia (CAP) has always been a disease characterized by educated guesswork. As pathological confirmation of pneumonia is rarely obtained, the diagnosis of CAP is a presumptive one based on the history, clinical signs, and a chest X-ray deemed consistent with acute consolidation (1). Because the pathogen is almost never known at the time treatment commences, educated guesswork (based on the most locally applicable etiological studies) is further employed to select the most appropriate antibiotic therapy (1).

Implicit in our whole approach to CAP is that sometimes we do get the diagnosis wrong. There are a variety of rarer diseases that may present like CAP. An initial chest X-ray may not show infiltrates easily apparent 24–72 hours later. Occasionally, chronic changes on chest X-ray may be misinterpreted as acute pathology. Despite these limitations, the general perception of clinicians is that we get the diagnosis of CAP right most of the time, and not only have we become comfortable with our empiric approach to therapy but also, health payers are comfortable with higher reimbursements for pneumonia than other nonspecific respiratory infections, and CAP is one of the most stringently monitored conditions with respect to quality-of-care measures.

In this issue of the *Journal*, Claessens and colleagues (pp. 974–982) present their study of 319 patients with a clinical diagnosis of CAP who had both a chest X-ray and a thoracic computed tomography (CT) scan at the time of admission (2). Disturbingly, 30% of patients who were felt to have CAP based on the presentation and chest X-ray had no evidence of pneumonia on CT scan. Furthermore, one third of patients who had no change on chest X-ray had CT changes consistent with pneumonia. Overall, the CT scan results showed that the combination of clinical features and chest X-ray lead to a misdiagnosis of the absence or presence of CAP in nearly one-third of all patients studied, and clinicians adjusted their perception of the likelihood of CAP being the diagnosis in more than 50%. If confirmed by further studies, this shifts the assessment of the diagnosis of CAP from "we might occasionally get it wrong" to "Houston, we have a problem." The implications for everything from empiric therapy to reimbursement and quality of care measures are enormous.

Is a CT scan is an adequate gold standard for the diagnosis of pneumonia? There are no studies correlating CT scan results with pathology in the setting of CAP, nor are there likely to be in anything other than severe, fatal disease. In the absence of data to the contrary, then, it seems reasonable to accept CT evidence of consolidation as the gold standard. Although advances in CT scanning have dramatically reduced the acquisition time, cost, and radiation exposure such that modern generations of machines could perceivable replace plain radiography during the next decade, for the time being, a plain chest X-ray will remain the primary diagnostic tool.

How, then, should clinicians respond to the challenge from Claessens and colleagues that we are getting the diagnosis wrong in a third of our patients?

First, we should be reassured that selection of antibiotic therapy is still based on etiological data from studies on patients that other clinicians were comfortable calling CAP. If we are getting it wrong now, there are no data to suggest key etiological studies were getting it more or less wrong before, so the studies are still valid and there is no urgent need to change our approach. Moving forward, we are going to need to know whether CT-positive, chest X-ray (CXR)-negative CAP has the same prevalence of pathogens and the same clinical outcomes as CT-positive, CXR-positive disease. Equally we will need to know whether patients deemed to have CAP but with a subsequent negative CT scan have different pathogens or outcomes. These will be critical questions to not just clinicians but also health-payers and those focused on quality-of-care metrics.

Are there any patients in whom a CT scan should be currently performed at admission, based on the data from Claessens and colleagues (2)? It was notable that the only real predictors of pneumonia being present on a CT scan in the setting of a negative chest X-ray were the presence of unilateral crackles and a very high C-reactive protein (CRP). Examining patients thankfully remains important. Conversely, lower CRP levels were really the only helpful marker of a potential false-positive chest X-ray diagnosis. Interestingly, in the setting of both false-positive and false-negative chest X-rays, procalcitonin was not a discriminator, and although there were small differences in the white cell count, these differences were unlikely to be clinically helpful.

Finally, it is worth reflecting on why clinicians may be overcalling the diagnosis of CAP based on chest X-rays. In the right clinical context, convincing ourselves that pneumonia might be present based on soft radiological changes allows us to go down a well-validated clinical pathway. If we decide soft radiological changes are not pneumonia, then we have no clear clinical pathways, no metrics to tell us quality of care is being met, and in some settings, possibly reimbursement issues. Although radiologists and research studies like to talk in terms of probability of pneumonia (definite, probable, possible) for clinicians, health-payers, and quality-of-care metrics, the patient either does or does not have CAP. What we need is as clear data on what to do if we have a CAP-like syndrome but decide pneumonia is not present on CXR as we have for when it is.

If we really are getting the diagnosis wrong as often as Claessens and colleagues suggest we are (2), then we need to start back at the beginning and redefine the etiology and outcomes of patients with CAP-like presentations based on a CT gold standard overriding the chest X-ray interpretation. In this respect, I cannot help but wonder whether older categorizations we have largely abandoned, such as lobar pneumonia and bronchopneumonia, will come back as we try to better define subgroups of patients, especially those in whom the chest X-ray is sufficient and a CT scan not required. I am, however, quite sure that questioning the fundamental diagnosis of CAP is now a major consideration when studies produce differing results, and much of what we think is true now needs to be reevaluated in the light of how new technology can better inform us of what is really going on in individual patients. ■

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Spotlight on Inflammation in Pulmonary Hypertension

Two articles in this issue of the *Journal*, by Kumar and colleagues (pp. 998–1008) (1) and Le Hiress and colleagues (pp. 983–997) (2), provide new insights on how inflammatory processes can cause pulmonary arterial hypertension (PAH). The articles focus on the injury response in the pulmonary artery that causes pulmonary arterial remodeling with increased smooth muscle cells, a fibrotic response, and increases in the pulmonary artery and right ventricular systolic pressures.

The work of Le Hiress and colleagues (2) focused on how the responses of endothelial cells to injury can initiate inflammation in pulmonary hypertension (Figure 1). The injury was induced by hypoxia or monocrotaline exposure in rats. Previously, macrophage inhibitory factor (MIF) has been implicated in pulmonary artery remodeling and pulmonary hypertension (3–5). Le Hiress and colleagues (2) identified MIF and CD74 as critical regulators of inflammatory signals in endothelial cells, controlling the expression of specific adhesion molecules, cytokine mediator molecules, and leukocyte migration. The same molecular network of MIF/CD74 was up-regulated in the pulmonary artery tissues of humans with idiopathic or heritable PAH (iPAH, hPAH).

Kumar and colleagues (1) focused on *Schistosoma*-induced PAH in humans and the experimental model in mice. Th2 responses, with IL-4 and IL-13 as prominent mediators, are known to be an important component of the immune response to infection with schistosome parasites (6) and have been previously reported to be important for PAH in the experimental model (7, 8). Kumar and colleagues (1) studied the inflammatory cell aspect of the process (Figure 1) and showed that bone marrow cell-derived IL-4 and IL-13 were critical determinants of the pulmonary hypertension phenotype in mice. Further, the authors showed that the IL-4/IL-13 axis is increased in human schistosomiasis-associated PAH lungs.

Kumar and colleagues (1) demonstrated that transforming growth factor β (TGF-β) signaling was amplified by the excess IL-4/IL-13 produced in response to *Schistosoma* egg exposures. It is of note that schistosomiasis-associated PAH can persist in humans even after antihelminthic treatment and an inability to detect active infection (9).

We do not know whether and how the mechanisms of inflammation in PAH studied by Le Hiress (2) and colleagues and Kumar and colleagues (1) are linked. The two research groups studied separate experimental models and separate human PAH forms. For example, it is entirely possible that in the IL-4/IL-13–dependent process that causes PAH, the CD74/MIF axis has no critically important role, and vice versa. The two studies (1, 2) identified shared cell types (T cells), processes (inflammatory cell migration), and mediators (IL-6). Figure 1 illustrates several additional potential connections. CD74 has at least two cellular functions: it is the invariant chain of major histocompatibility complex class II (MHCII) protecting the MHCII molecule during assembly in the endoplasmic reticulum, and it is a receptor for MIF. MIF is also a multifunctional soluble mediator that helps to retain macrophages in the tissue and that controls inflammation. Le Hiress and colleagues (2) identified T cells in the lung tissue of patients with PAH as the producers of MIF. Kumar and colleagues (1) found that macrophages responded to the IL-4/IL-13–initiated process by activating TGF-β. Previous studies have shown that mice deficient in CD74 or MIF, or mice treated with a MIF inhibitor, have highly significantly depressed IL-4/IL-13 responses (10, 11).

The molecular networks studied by Le Hiress and colleagues (2) and Kumar and colleagues (1) could also be linked via the adhesion molecules that were up-regulated in the endothelial cells (Figure 1). Le Hiress and colleagues (2) found that the MIF/CD74 axis controlled the increased expression of several adhesion molecules, among them vascular cell adhesion protein 1 (VCAM-1), and the authors detected increased P-selectin expression by pulmonary artery endothelial cells from iPAH and hPAH lungs. IL-4 and IL-13 signaling, the critical event for PAH studied by Kumar and colleagues (1), is known to significantly induce both VCAM-1 (12) and P-selectin (13) on endothelial cells. Further, Kumar and colleagues (1) found that the migration of bone marrow–derived leukocytes that were capable of producing IL-4 and IL-13 was necessary for the development of experimental PAH. Le Hiress and colleagues (2) showed that MIF/CD74–induced up-regulation of adhesion molecules on

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ORIGINAL ARTICLE

Early Chest Computed Tomography Scan to Assist Diagnosis and Guide Treatment Decision for Suspected Community-acquired Pneumonia

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Abstract

Rationale: Clinical decision making relative to community-acquired pneumonia (CAP) diagnosis is difficult. Chest radiograph is key in establishing parenchymal lung involvement. However, radiologic performance may lead to misdiagnosis, rendering questionable the use of chest computed tomography (CT) scan in patients with clinically suspected CAP.

Objectives: To assess whether early multidetector chest CT scan affects diagnosis and management of patients visiting the emergency department with suspected CAP.

Methods: A total of 319 prospectively enrolled patients with clinically suspected CAP underwent multidetector chest CT scan within 4 hours. CAP diagnosis probability (definite, probable, possible, or excluded) and therapeutic plans (antibiotic initiation/discontinuation, hospitalization/discharge) were established by emergency physicians before and after CT scan results. The adjudication committee established the final CAP classification on Day 28.

Measurements and Main Results: Chest radiograph revealed a parenchymal infiltrate in 188 patients. CAP was initially classified as definite in 143 patients (44.8%), probable or possible in 172 (53.8%), and excluded in 4 (1.2%). CT scan revealed a parenchymal infiltrate in 40 (33%) of the patients without infiltrate on chest radiograph and excluded CAP in 56 (29.8%) of the 188 with parenchymal infiltrate on radiograph. CT scan modified classification in 187 (58.6%; 95% confidence interval, 53.2–64.0), leading to 50.8% definite CAP and 28.8% excluded CAP, and 80% of modifications were in accordance with adjudication committee classification. Because of CT scan, antibiotics were initiated in 51 (16%) and discontinued in 29 (9%), and hospitalization was decided in 22 and discharge in 23.

Conclusions: In CAP-suspected patients visiting the emergency unit, early CT scan findings complementary to chest radiograph markedly affect both diagnosis and clinical management.

Clinical trial registered with www.clinicaltrials.gov (NCT 01574066).

Keywords: emergency medicine; community-acquired pneumonia; diagnosis; multidetector CT scan; chest radiograph

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At a Glance Commentary

Scientific Knowledge on the Subject: Community-acquired pneumonia diagnosis is a daily challenge whose definition relies on clinical signs and radiograph abnormalities. Chest radiograph lacks sensitivity and specificity.

What This Study Adds to the Field: Chest computed tomography scan improves diagnosis and alters management in emergency patients with suspected community-acquired pneumonia.

Community-acquired pneumonia (CAP) is frequently diagnosed in emergency patients (1, 2). CAP mostly occurs in elderly and frail patients (3, 4), and often leads to life-threatening conditions with an overall 30-day mortality rate of 10% in adults (3). Because delayed treatment impairs prognosis, early diagnosis is necessary to administer antimicrobials in a timely manner (5). The gold standard for diagnosis of CAP should be detection of the microorganisms in the lung tissue (6), which is seldom feasible in everyday practice and requires 48 hours for results.

Clinical CAP diagnosis is often uncertain. Misdiagnosis is frequent and leads to delayed antimicrobial therapy (5) or overuse of antibiotics (7). An operational definition has been established to help physicians diagnose CAP (8). Lacking alternative explanations, CAP should be suspected in patients with systemic signs of infection, symptoms of acute lower respiratory tract infection, and new focal chest symptoms on examination (8). However, combining clinical signs and symptoms has limited value (9, 10).

Because of the difficult clinical decision making in CAP diagnosis, the presence of parenchymal lung disease determination, a requirement for pneumonia diagnosis, is based on evidence of parenchymal infiltrate on chest radiograph (8). However, significance of radiograph abnormalities remains debatable because of a considerable risk of missing or overdiagnosing CAP (11, 12). Concordance of interpretation on the presence of parenchymal infiltrate is poor, whatever practitioners' experience and qualifications (13–16). Furthermore, appearance of infiltrate can be delayed and performance of chest radiograph distorted by coexisting comorbidities (17–19). Therefore, chest radiograph seems an imperfect gold standard for CAP in the context of emergency diagnosis process; nonetheless, it is currently used.

Some authors advocate the use of computed tomography (CT) scan when standard imaging is inconclusive (8, 9, 20). Additional data support the use of CT scan (21) to improve sensitivity of CAP diagnosis (21). Chest CT scan could thus help to better determine diagnosis.

Almost all major decisions regarding CAP management, including diagnostic and treatment issues, rely on the initial assessment (20). Because suspected CAP patients often are seen in the emergency department, developing strategies that improve early management is essential. Here we explore the impact of systematic early chest CT scan on diagnosis in patients visiting the emergency department with clinically suspected CAP, and on their management according to standard of care.

Methods

Setting

We conducted a multicenter, prospective, interventional study, entitled Early CT-Scan for Community-Acquired Pneumonia at the Emergency Department (ESCAPED), from November 2011 to January 2013, in four emergency units of tertiary teaching hospitals.

The study was supported by grants from the French Ministry of Health (PHRC AOM 10118), sponsored by Assistance Publique–Hôpitaux de Paris, and monitored by the Clinical Research Unit Paris Centre. The French health authorities (ANSM) and the institutional review board for the protection of human subjects (Paris No. 2011-oct-12749) approved the study protocol and patient informed consent procedures. All enrolled patients provided written informed consent before inclusion.

Objectives

The primary objective was to measure the impact of multidetector chest CT scan on the probability of CAP as estimated by the attending emergency physician. To assess the study's primary endpoint, we determined how often the clinical judgment of the physician was modified by the results of multidetector chest CT scan.

The secondary objectives were to assess how multidetector chest CT scan influenced the management of the patient (i.e., prescription of antimicrobial therapy and decision on site-of-care [admission or discharge] by the attending emergency physician), to describe multidetector chest CT scan results as compared with chest radiograph, to estimate whether multidetector chest CT scan led emergency physicians to properly classify patients as compared with an adjudication committee judgement, and to determine the factors associated with final adjudicated diagnosis of CAP based on chest CT independently of CAP category.

Study Population

Consecutive adults (>18 yr) were enrolled if the attending emergency physician clinically suspected CAP. Clinical suspicion of CAP was based on investigator's judgment in patients that fulfilled the following criteria: new onset of systemic infection (at least one among sweat, chills, aches and pain, temperature ⩾38°C or <36°C) and symptoms of an acute lower respiratory tract infection (at least one among cough, sputum production, dyspnea, chest pain, altered breathing sounds at auscultation) (8). Pregnant women, patients in palliative care or with anticipated barriers to completing follow-up data collection, patients classified three or higher according to the CRB65 score (22), and those requiring intensive care for any purpose because of specific management of critically ill CAP patients were not eligible. Because of organizational constraints, patients could only be enrolled from Monday to Friday (8:00 A.M.–6:00 P.M.).

Patient Management and Data Collection

Patient management was based on current recommended practice guidelines. Recorded baseline data consisted of demographic data, coexisting illnesses, clinical findings, and laboratory tests.

Interpretation of Radiologic Data and CT Scan

Chest radiograph was performed using a standardized protocol. Conversely to most studies on CAP, inclusion criteria were based on clinical features solely; therefore,

results of chest radiograph did not preclude inclusion. Characteristics of chest radiographs were recorded by the local radiologist on a dedicated form that specified position (standing, sitting, prone); views (front, profile); technical quality (good, fair, poor); and description of parenchymal, pleural, and mediastinum abnormalities. The radiologist established the radiologic CAP probability solely based on chest radiographs (high, intermediate, low, ruled out).

Multidetector chest CT scan was performed, as soon as possible after chest radiographs and after pre–CT scan evaluation questionnaire, ideally within the 4 hours following inclusion. A low-dose protocol was recommended. Contrast material was injected at the local radiologist's discretion. CT scan was interpreted by the local radiologist who, in addition to usual description, indicated on a dedicated form the level of radiologic CAP probability according to the CT scan criteria (*see* the online supplement). The local radiologist was aware of CAP suspicion and patient history but of no other data.

To identify the patients for whom chest CT scan may be most beneficial in diagnosing or excluding pulmonary infiltrate, we compared the characteristics of patients using cross-tabulation according to the presence or absence of infiltrate on chest radiograph and results of chest CT scan.

CT Scan Diagnostic and Therapeutic Impact Assessment

Immediately before CT scan, the emergency physician filled in a standardized report form including patient history, laboratory data, and both his own interpretation and standardized interpretation of the chest radiograph by the local radiologist. The physician, aware of the interpretation of the chest radiograph by the local radiologist, established pre–CT scan probability of CAP diagnosis according to a four-level Likert scale (definite, probable, possible, excluded) and outlined an antimicrobial therapy plan and the site-of-care for patient management. This diagnosis classification does not correspond to a validated CAP classification but to the practitioner's global confidence in CAP diagnosis.

Immediately after viewing the CT scan results, the same physician completed the standardized case report form and rated the post–CT scan probability of diagnosis of CAP according to the Likert scale, and outlined an antimicrobial therapy plan and site-of-care (admission or discharge). Based on post–CT scan evaluation, patients were discharged or admitted to the hospital on an appropriate unit and treated according to unit procedures.

Adjudication Committee

The adjudication committee involved three independent experts in infectious diseases, pneumology, and radiology within a panel of nine experts, masked to emergency investigators' rating. For each patient, the adjudication committee established two CAP probabilities. First, based on data collected in the baseline standardized case report forms, images of radiographs and multidetector CT scan recorded on a dedicated DVD, the adjudication committee retrospectively assigned the probability of CAP diagnosis using the four-level Likert scale (hereafter referred to as "After CT scan adjudication committee CAP probability"). Second, the adjudication committee assigned a final probability of diagnosis of CAP, using all available follow-up data including patients' discharge summary and a telephone follow-up by assistant investigators with the patient, relatives, or general practitioners at Day 28 (hereafter referred to as "Day-28 adjudication committee CAP probability"). In patients lost to follow-up, post–CT scan CAP adjudication committee classification was carried forward. This Day-28 adjudication was used as the gold standard in the study.

Statistical Analyses

Baseline and follow-up characteristics were described by means (SD) or median (interquartile range) for continuous variables normally distributed or with skewed distribution, respectively, and by percentages for categorical variables.

We performed chi-square or Fisher exact tests as appropriate for qualitative variables, and the Wilcoxon/Mann-Whitney test for continuous variables with skewed distributions to compare baseline patient characteristics and study outcomes between groups.

We considered that each modification of at least one category in the four-level Likert scale was a change in diagnosis, whatever the direction of the change (increase or decrease in the CAP probability level). To estimate whether chest CT scan helped emergency physicians to properly reclassify patients according to the adjudication committee's final probability of diagnosis for CAP (gold standard), we calculated the net reclassification index (NRI) (23), thus dichotomizing the CAP level of certainty: patients with high probability (definite/probable) and low probability (possible/excluded).

Factors associated with final adjudicated diagnosis of CAP based on chest CT were analyzed using multivariable logistic regression. Variables were selected to enter the model if associated with outcome with a P value less than 0.10 in bivariate analysis. A stepwise backward procedure, based on the Akaike information criteria, was used to select the final adjusted model.

All tests were two-sided; P values less than 0.05 were considered to denote statistical significance. All statistical analyses were performed using SAS software V9.3 (SAS Institute, Cary, NC).

Sample Size

In a previous study (21), prevalence of CAP changed from 38.3% before CT scan to 55.3% after CT scan; bilateral infiltrates changed from 12.8% before CT scan to 34% after CT scan. Therefore we hypothesized that multidetector CT scan would modify diagnosis probability level of certainty in 20% of patients. We calculated that 300 patients would allow the estimation of diagnosis change prevalence, with a 95% confidence interval (CI), at 15–25%.

Results

Characteristics of Participants and Pre–Chest CT Scan CAP Classification

For the study period, 319 patients were available for analysis out of 333 included in the ESCAPED study (Figure 1). Characteristics of the participants appear in Table 1. Sex ratio was approximately one. Over half of the patients (56%) were 65 years of age or older. Significant underlying disorders were recorded in 195 (61%), including 89 (28%) pulmonary disorders. Cough (n = 240; 76%) and dyspnea (n = 229; 72%) were frequent. Unilateral crackles were detected in 105 (33%). Parenchymal infiltrate (unilateral and bilateral) were described on chest radiograph in 188 (61%). In seven patients, chest radiograph

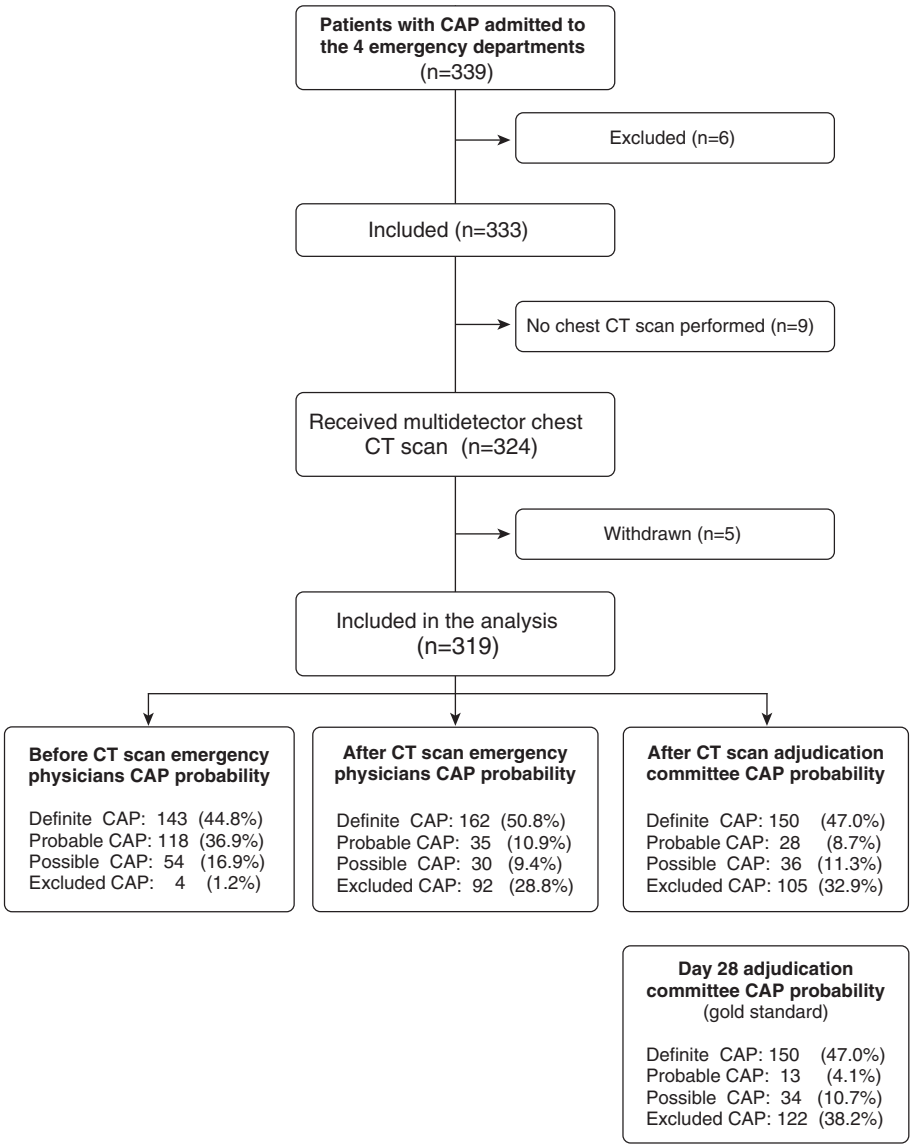

Figure 1. Flow chart. CAP = community-acquired pneumonia; CT = computed tomography.

was performed within 24 hours preceding emergency department visit. In the 312 remaining patients, local radiologists considered that chest radiograph probability for CAP diagnosis was high, intermediate, and low in 80 (25.6%), 88 (28.2%), and 118 (37.8%) patients, respectively, and ruled out in 26 (8.3%) patients (*see* Table E1 in the online supplement). Based on the pre–CT scan evaluation, the emergency physician classified CAP diagnosis as definite in 143 patients (44.8%), probable in 118 (37.0%), possible in 54 (17.0%), and excluded in four (1.2%).

Chest CT Scan Results

The main findings of the chest CT scan are summarized in Table 2 and Table E2. Radiologists considered that the probability for CAP diagnosis based on CT scan was high, intermediate, and low in 138 (43.2%), 38 (11.9%), and 37 (11.6%) patients, respectively, and ruled out in 105 (32.9%).

In the 120 patients out of the 308 patients with both completed interpretation by the local radiologist of chest radiograph and CT scan, and without any parenchymal infiltrate on chest radiograph, CT scan revealed parenchymal infiltrates compatible with CAP in 40 patients (33%; 13% of the 308 patients). As compared with the 80 patients without infiltrates on chest CT scan, these 40 patients tended to be older than 65 years (62.5 vs. 45.0%; $P = 0.0707$), were more likely to present crackles (48.7 vs. 26.6%; $P = 0.0169$), to have higher C-reactive protein (CRP) levels (138.1 vs. 59.9 mg/L; $P = 0.0037$), and higher white blood cell counts (12.3 vs. 10.2 $10^3/mm^3$; $P = 0.0387$) (*see* Table E3).

Among the 188 out of the 308 patients with a parenchymal infiltrate on chest radiograph, CT scan excluded pneumonia in 56 patients (29.8%; 18% of the 308 patients). As compared with the 132 patients with infiltrates on chest CT scan, these 56 patients were older (71.1 vs. 63.2 yr; $P = 0.0131$), had lower white blood cell counts (10.2 vs. 12.6 $10^3/mm^3$; $P = 0.0283$), lower CRP levels (163.3 vs. 78.0 mg/L; $P = 0.0074$), and were more likely to have urea levels above 11 mM/L (25.0 vs. 11.4%; $P = 0.0179$) (*see* Table E4).

In the 85 patients with unifocal parenchymal infiltrate on chest radiograph, CT scan revealed multifocal infiltrates in 44 (51.8%). Table 3 presents the cross-tabulation of chest radiograph and CT scan CAP results.

Impact of the Chest CT Scan on the Emergency Physicians' Agreement with Diagnosis of CAP

Based on the CT scan evaluation, the emergency physician modified the probability for CAP diagnosis in 187 participants (58.6% [95% CI, 53.2–64.0%]). Classification was upgraded in 59 (18.4%) patients (including two excluded cases before CT scan that were reclassified as definite). Among the 162 post–CT scan definite CAP, 55 (34%) were changed to definite CAP because of CT scan. Classification was downgraded in 128 (40.4%) patients (including 11 out of 36 definite cases before CT scan that were reclassified as excluded). CAP was excluded in 28.8% of participants after chest CT scan (Table 2, Figure 1).

Intermediate (probable-possible) diagnostic categories were more subject to modification (76.7% [95% CI, 70.4–83.1%]) than those with a high degree of certainty (definite-excluded) (17% [95% CI, 10.9–23.1]) (for details, *see* Table E4).

Adjudication Committee Classification

Ten patients were lost to follow-up and their post–CT scan classification was carried forward for the final classification. The "after CT scan adjudication committee CAP probability" and the "Day-28 adjudication committee CAP probability" are presented in Table 2 and Figure 1.

Table 1. Characteristics of the 319 Patients Included in ESCAPED Study

Characteristics	No. (%) or Mean ± SD (*n = 319*)
General characteristics	
Age	
Mean, yr	64.7 ± 20.0
⩾65 yr	177 (55.5)
Sex	
Female	164 (51.4)
Male	155 (48.6)
Nursing home resident	12 (3.8)
Background and vaccinations	
Comorbidities	
At least one comorbidity	195 (61.1)
Chronic respiratory disease	89 (28.0)
COPD	64 (20.1)
Asthma	46 (14.4)
Congestive heart failure	39 (12.3)
Diabetes	51 (16.0)
Kidney disease	36 (11.3)
Neoplasia	32 (10.0)
Liver disease	15 (4.7)
History of stroke	12 (3.8)
Vaccination status	
Influenzae vaccination during the past year	118 (40.0)
Pneumococcal vaccination	45 (16.5)
CAP characteristics at inclusion	
Previous antibiotic treatment	111 (34.8)
Symptom duration before visiting emergency unit, d	
In all patients (n = 319)	7.4 ± 10.5
In antibiotic treatment-naive patients (n = 208)	5.5 ± 9.5
In patients with prior antibiotic treatment (n = 111)	10.8 ± 11.2
Signs and symptoms in the emergency unit	
Cough	240 (75.7)
Chest pain	103 (32.4)
Sputum production	147 (46.2)
Dyspnea	229 (71.8)
Respiratory rate > 30/min	42 (13.2)
Crackles	105 (33.2)
Chills	96 (30.2)
Headaches	51 (16.0)
Myalgia	59 (18.6)
Fever	112 (35.3)
Confusion	12 (3.8)
Heart rate > 125/min	24 (7.5)
Systolic blood pressure <90 mm Hg	4 (1.3)
Diastolic blood pressure <60 mm Hg	26 (8.2)
PSI risk class	
I	49 (15.4)
II	83 (26.0)
III	69 (21.6)
IV	90 (28.2)
V	28 (8.3)
CRB65 score*	
1	149 (46.7)
2	47 (14.7)
3	5 (1.6)
4	0 (0.0)
Biologic data	
White blood cell, 10^3/mm^3	11.5 ± 5.6
Procalcitonin, μg/L	1.8 ± 5.3
CRP, mg/L	110.8 ± 107 0
Urea > 11 mmol/L	41 (12.9)
pH < 7.35	3 (0.9)
Pa_{O_2} < 60 mm Hg or Sa_{O_2} < 90%	49 (17.0)

(Continued)

NRI is presented in Table E5. For 100 patients (31.3%), the emergency physician changed the CAP probability level. Modifications of CAP probability level were adequate with the adjudication committee's final classification in 80 out of 100 (80.0% of the modifications; 25.1% of the total population; NRI = 0.39). Most modifications (70%) consisted in appropriate downgrading of diagnosis probability from definite/probable CAP to low probability (possible/excluded), whereas 10% consisted in appropriate diagnosis upgrading (from low probability to high probability). In 20 out of 100 patients, reclassification was inadequate (Table 2).

Factors Associated with Adequate Reclassification of CAP Probability Based on Multidetector Chest CT Scan

In bivariate analysis, few parameters differed between the 80 participants with adequate reclassification and the remaining 239 (219 without changes, 20 with inadequate reclassification) (*see* Table E6). According to the multivariate analysis, CAP probability was adequately changed by multidetector chest CT scan results if pre–CT scan diagnosis was "probable" (60% of probable cases being downgraded) and the absence of parenchyma infiltrate on chest radiograph (Table 4).

Impact of Chest Multidetector CT Scan on Antimicrobial Therapy and Decision for Site of Care

Before CT scan, antimicrobial agents were initiated in 207 (64.8%) patients. After CT scan, administration of antimicrobial agents was stopped in 29 (14.0%) of these 207 patients. Conversely 51 (45.5%) of 112 patients without initial antimicrobial therapy were given antibiotics after CT scan results. CT scan led to initiation of anticoagulation for pulmonary embolism in three patients, and diuretics for cardiac failure in 11 patients.

CT scan also induced a modification in decisions for site-of-care. A total of 45 (14.1%) changed categories: 22 outpatients were finally admitted, and 23 admissions changed for discharge. Modifications in antimicrobial treatments, including changes in pharmacologic classes, and of site-of-care were observed in 194 (60.8%).

Discussion

In this prospective study, we assessed the effect of early chest multidetector CT scan

Table 1. (*Continued*)

Characteristics	No. (%) or Mean ± SD (*n* = *319*)
Radiologic data	
Parenchymal infiltrate	188 (61.0)
Including unilateral finding	128 (71.9)
Including bilateral finding	50 (28.1)
Pleural effusion	84 (26.4)
CAP management	
28-d mortality	13 (4.1)

Definition of abbreviations: CAP = community-acquired pneumonia; COPD = chronic obstructive pulmonary disease; CRP = C-reactive protein; ESCAPED = Early CT-Scan for Community-Acquired Pneumonia at the Emergency Department; PSI = pneumonia severity index.
*CRB65 is a CAP severity score taking into account confusion, respiratory rate, blood pressure, and age 65 or older.

on clinical decision in patients with clinically suspected CAP visiting emergency units. CT scan modified CAP probability level by emergency physicians in over half of the patients, 80% of these modifications were in accordance with adjudication committee final CAP classification, and led to modifications of medical decisions in two-thirds. These modifications involved patients with clinically suspected CAP and either parenchymal infiltrate on chest radiograph (for one-third of whom CT scan excluded CAP), or those without infiltrate for whom the discovery of the infiltrate on CT scan, also in one-third, made possible the establishment of CAP diagnosis and the initiation of the adequate therapy. Characteristics of patients that benefit from chest CT scan to confirm or to rule out CAP diagnosis differed from those that did not.

Diagnosing CAP currently relies on the combination of systemic and lower respiratory tract symptoms of infection associated with new infiltrates on chest radiograph (8). For this study, we purposely decided to include patients based on initial clinical features, without results of the radiographs, to measure the positive impact of CT scan even in patients with normal chest radiograph. Thereby we challenged the performance of chest radiograph for CAP diagnosis. Despite this specific point, characteristics of patients included in this study are comparable with those reported in the literature. The exclusion of highest CRB65 categories in the ESCAPED study, limiting inclusion of patients older than 65 (22), may explain that mean age (65 yr) falls within the lower values of those reported elsewhere. Previous history of respiratory disorders, cancer, and congestive heart failure was frequent (2, 3, 10, 17, 19). Therefore, we believe that our results can be extrapolated to most emergency patients with suspected CAP who could benefit from CT scan.

To measure the effect of CT scan on CAP probability, we asked the emergency physicians to rate the probability of CAP based on their own judgement (taking into account history, clinical and biologic data, the standardized interpretations of chest radiograph, without and then with multidetector chest CT scan by the local radiologist), using a Likert scale. This classification did not rely on a validated scale, as in other infectious diseases, such as endocarditis (24). However, we believe this classification based on doctor self-assessment to make sense. Such a hypothesis has been raised for pulmonary embolism pretest probability, especially for experienced physicians (25).

Table 2. Distribution of Changes in Emergency Physicians' Estimation of the Probability Level of CAP before and after Chest CT Scan in 319 Patients

	Physician CAP Probability Level after Chest CT Scan					Changes in Classifications	
	Definite	Probable	Possible	Excluded	Total	Number	Modification Rates (95% CI)
Physician CAP probability level before chest CT scan							
Definite	**107**	15	10	11	143 (44.8%)	36	25.2% (18.1–32.3)
Probable	41	**16**	13	48	118 (36.9%)	102	86.4% (80.3–92.6)
Possible	12	4	**7**	31	54 (16.9%)	47	87.0% (78.1–96)
Excluded	2	0	0	**2**	4 (1.25%)	2	50.0% (1.0–99.0)
Total	162 (50.8%)	35 (10.9%)	30 (9.4%)	92 (28.8%)	319	187	58.6% (53.2–64.0)
Adjudication Committee CAP Probability after CT Scan							
	150 (47.0%)	28 (8.7%)	36 (11.3%)	105 (32.9%)			
Day-28 Adjudication Committee CAP Probability							
	150 (47.0%)	13 (4.1%)	34 (10.7%)	122 (38.2%)			

Definition of abbreviations: CAP = community-acquired pneumonia; CI = confidence interval; CT = computed tomography.
Bold values correspond to CAP probability level unmodified by CT scan.

Table 3. Radiologic Probability of CAP in ESCAPED Study Patients with Chest Radiograph and CT Scan Local Interpretation

Parenchymal Infiltrate on Chest Radiograph	Chest CT Scan Probability of CAP		Total
	High or Intermediate*	Low or Ruled Out*	
Yes	**132**	56	188 (61.1%)
No	40	**80**	120 (38.9%)
Total	172 (55.8%)	136 (44.2%)	308 (100%)†

Definition of abbreviations: CAP = community-acquired pneumonia; CT = computed tomography; ESCAPED = Early CT-Scan for Community-Acquired Pneumonia at the Emergency Department. Bold values correspond to CAP diagnostic classification concordant using chest radiograph and chest CT scan.
*Level of CAP probability according to CT scan. High or intermediate chest CT scan probability of CAP: systematic alveolar condensation, or alveolar condensation with peripheral and localized ground glass opacities, or bronchiolar focal or multifocal micronodules; peripheral alveolar condensation, or retractile systematic alveolar condensation, or diffuse ground glass opacities. Low or ruled out chest CT scan probability of CAP: pulmonary infarct, pulmonary mass, or other abnormalities, or normal images.
†Seven out of the 319 patients did not have their chest radiograph interpreted by the local radiologist, and final conclusion of chest radiograph and/or CT scan was not completed in four others.

Overall, CT scan led to better practitioner confidence in CAP diagnosis. The upgrading of CAP diagnosis level of certainty in 18.4% reveals the low sensitivity of chest radiograph for diagnosing CAP. This is particularly important in the subgroup of patients with clinically suspected CAP but without parenchymal infiltrate on chest radiograph (*stricto sensu*, non-CAP patients) for one-third of whom the discovery of infiltrate on CT scan suggests CAP diagnosis. Furthermore, in patients with definite/probable chest radiograph, CT scan allowed better staging of the pulmonary involvement (discovery of multifocal or bilateral localizations), identifying localizations or complications undiagnosed by chest radiograph. Conversely, CT scan also underscored the low performance of chest radiograph in the 40% of patients for whom CT scan results led to downgrading of the CAP level of certainty, including patients with definite CAP who were excluded after CT scan. Overall, one-third of the CAP cases was excluded after CT scan. In all these patients, early CT scan corrected patients' diagnosis and avoided diagnostic and treatment red herrings. Of note, post–CT scan CAP classification performed at Day 1 was confirmed at Day-28 evaluation in 80%, revealing CT scan reliability in early evaluation.

Furthermore, CT scan results not only induced diagnosis probability changes but also led to immediate adjustment of patients' care. Alternative diagnoses to CAP were mainly exacerbation of chronic obstructive pulmonary disease (16%) and acute heart failure (16%) as reported in the current literature (26). We acknowledge that the appropriateness of treatment \changes based on CT scan results may be debatable. Recommendations for daily practice are developed from studies using radiographs for standard diagnosis (8). Therefore, whereas CT scan improved diagnosis of CAP, it is unclear whether it also results in better outcome. Indeed, ESCAPED was not designed to assess the impact on outcome of performing a multidetector chest CT scan; however, it is probable that the initiation of antibiotic in patients for whom CT scan established CAP diagnosis had a positive impact on their outcome.

Despite systematic CT scan, the experts of the adjudication committee were unable to provide firm diagnosis (definite or excluded) at Day 28 in some patients. This underscores how difficult the diagnosis of CAP is even using better quality imaging. Whereas the best diagnosis for infection should be the proof a pathogen in a usually sterile tissue, this is seldom possible in daily practice for CAP patients in whom microbiologic results are frequently negative (27). Whereas new biologic tools may also help (28), current recommendations do not support routine use of biomarkers to assist diagnosis of CAP, and new microbiologic techniques have seldom been evaluated. We also agree that patients without infiltrate observed on radiograph and with unsure diagnosis greatly benefited from CT scan. However, we also observed significant changes in several patients with radiograph abnormalities.

Table 4. Factors Associated with Adequate Reclassification of CAP Probability Based on Multidetector Chest Computed Tomography in the 319 Patients of the ESCAPED study (Multivariate Analysis)

	OR (95% CI)*	*P* Value†
Sex		
Female	1.00	
Male	1.60 (0.87–2.92)	0.13
Previous antimicrobial therapy		
No	1.00	
Yes	0.57 (0.30–1.08)	0.09
Physicians' agreement for diagnosis		<0.001
Definite	1.00	
Probable	6.43 (3.21–12.88)	<0.001
Possible	0.79 (0.28–2.22)	0.66
Excluded	3.55 (0.32–38.94)	0.30
Parenchyma infiltrate on chest radiograph		
Present	1.00	
Absent	2.97 (1.60–5.50)	<0.001
Unilateral crackles		
No	1.00	
Yes	1.76 (0.90–3.43)	0.10

Definition of abbreviations: CAP = community-acquired pneumonia; CI = confidence interval; ESCAPED = Early CT-Scan for Community-Acquired Pneumonia at the Emergency Department; OR = odds ratio.
Adequate reclassification corresponded to perfect adequation with final adjudication committee diagnosis of CAP.
*Results are presented as OR and 95% CI.
†*P* values below 0.05 were statistically significant.

Our results suggest that many patients with suspected CAP would benefit from CT scan, although this strategy may encounter some barriers. Use of CT scan necessitates exposure to radiation and thus might be harmful. For the study's purpose, the protocol recommended using a low-dose CT scan, with an estimated radiation dose corresponding to 250 mGy.cm (dose length product; i.e., twice the natural radiation received each year in Western countries). However, improvement in reconstruction methods reduces CT scan radiation to levels of a standard chest radiograph and allows adequate quality for parenchymal study (29). Another barrier is the cost effectiveness of the procedure, which was not addressed in the present study. CAP management-related costs vary with site-of-care (30). We observed that CT scan modified (14%) the site-of-care in few patients. On the one hand, CT scan allowed discharge of these initially admitted patients, limiting cost of treatment. On the other hand, it permitted admission of patients for whom delayed treatment would have had a negative medical impact. However, we cannot ascertain in this study whether CT scan is cost-effective. Finally, whereas availability may vary among hospitals, most emergency departments now have easy access to CT scan (31).

CAP presents an extensive clinical and radiologic spectrum (20). Beyond the difficulties of interpretation and interobserver discrepancies, chest radiograph results seemed, in a large number of cases, to inadequately guide emergency physicians, leading them toward making inappropriate decisions on both diagnosis and antimicrobial therapy for CAP-suspected patients, which raises concerns for a disease with a high 30-day mortality rate. The ESCAPED study suggests that a CT scan performed within the first hours facilitates early and accurate positive or negative diagnosis of CAP. A key question is the population that would most benefit from chest CT scan. We observed that CAP-suspected patients with negative chest radiograph but for whom chest CT scan reveals a parenchymal infiltrate (i.e., false-negative of chest radiograph) were more likely to have crackles or high inflammatory markers (CRP or white blood cells count). This suggested that patients will benefit from CT scan when chest radiograph is normal despite clinical signs and biologic markers evocating CAP. Conversely, those patients with positive chest radiograph and negative chest CT scan (i.e., false-positive of chest radiograph) had lower inflammatory markers (CRP or white blood cell count). In both conditions, older patients benefited from chest CT scan.

Here, early use of CT scan clearly outclassed chest radiograph and affected diagnosis, treatment, and decision for site-of-care in emergency patients with suspected CAP. Therefore, we believe that a strategy favoring CT scan as the preferred first imaging technique in targeted patients would improve diagnosis and may even, in the near future, reduce global radiation exposure by limiting unnecessary radiation cause by multiple procedures. Whether these modifications would improve outcome should be addressed in a randomized controlled trial. ■

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