Antibiotic Use in the Management of Pulmonary Nodules

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Background: Pulmonary nodules are common incidental findings on thoracic imaging examinations. This study sought to determine whether antibiotic use is associated with any improvement in nodule appearance and to identify clinical findings and nodule characteristics potentially influencing the decision to prescribe antibiotics.

Methods: Electronic medical records were reviewed of outpatients referred to a metropolitan cancer center for pulmonary nodules seen on chest CT scans who did not undergo biopsy. The primary end point was the appearance of each nodule on the first follow-up scan. A subset analysis was performed for patients manifesting symptoms or radiographic findings suggesting infection. An analysis was performed to determine what clinical and radiographic findings were associated with the decision to prescribe antibiotics.

Results: Between January 2003 and December 2004, 143 evaluations were performed for 293 nodules. Antibiotics were prescribed to 34 (24%) evaluations. A trend toward improvement was seen with antibiotic use, which was not significant. The percentage of nodules that improved was 33% among those receiving antibiotics and 27% among those who did not (odds ratio 1.33; 95% CI, 0.55-3.27). Among 63 patients with pulmonary symptoms, 41% of nodules improved among those receiving antibiotics and 28% among those who did not (odds ratio 1.78; 95% CI, 0.42-7.78). The decision to prescribe antibiotics was associated only with larger nodule size and bronchiectasis.

Conclusions: These data do not support antibiotic use for pulmonary nodules. However, the trend toward improved nodule appearance suggests that larger prospective trials are warranted to clarify the role of antibiotics in managing lung nodules.

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Abbreviation: ACCP = American College of Chest Physicians

Advances in CT scanning have revolutionized pulmonary medicine, allowing for the noninvasive diagnosis of multiple conditions of the lung and mediastinum that previously required biopsy. No technology, however, is without limits; widespread

acceptance of CT scanning has been complicated by the frequent finding of pulmonary nodules that are either too small for diagnostic biopsy or do not possess attributes specific to any single diagnosis. Lung cancer screening studies have shown that the likelihood of finding nodules at least 4 mm in diameter approaches 33% among otherwise healthy smokers.^{1,2} At least 150,000 nodules are detected annually in the United States.³ As technological advances allow for ever more sensitive imaging, pulmonary nodules are likely to endure as a significant clinical problem.

One common strategy in evaluating pulmonary nodules is obtaining follow-up CT scans at appropriate intervals, looking for changes in size.⁴ Guidelines published by the American College of Chest Physicians (ACCP) allow for serial imaging, especially among nodules thought unlikely to be malignant.

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Table 1—Characteristics of Study Population

Characteristic	All Evaluations	Receiving Antibiotics	Not Receiving Antibiotics	P Value
No. evaluations	143	34	109	
Average age, y	60	61.6	59.5	.25
Median age, y	61	60.9	61.1	.67
Male sex (%)	38 (27)	9 (26)	29 (27)	1.00
Prior malignancy (%)	67 (47)	15 (44)	52 (48)	.80
Ever smokers (%)	97 (68)	25 (74)	72 (66)	.53
Current smokers (%)	11 (11)	2 (8)	9 (12)	.72
Former smokers (%)	86 (89)	23 (92)	63 (88)	.72
Median pack-years	30	25	30	.61
Symptoms present	63 (44)	16 (47%)	47 (43%)	.70
Nodule number	293	72	221	...
Median nodule number per patient	2	2	2	.81
25th quartile	1	1	1	...
75th quartile	6	6	5	...
Median nodule size, mm	5	7	5	<.01
25th quartile	3	4	3	...
75th quartile	8.25	12	7	...
Median interval from initial CT to f/u CT scans, d	109	96	119	<.01

Data are presented in terms of number of evaluations. For current and former smokers, percentages are a function of all ever smokers. The *P* value refers to a comparison between the groups receiving antibiotics and the group not receiving antibiotics. f/u = follow-up.

While this strategy avoids any morbidity associated with invasive biopsy, it is not without risk. Performing multiple CT scans is expensive, burdensome to radiology centers, and results in significant radiation exposure. Moreover, anxiety associated with having an undiagnosed, potentially malignant abnormality can be considerable.

As many nodules may have an infectious cause, some advocate the use of empiric antibiotics, hoping that successful treatment may obviate the need for further testing. The Early Lung Cancer Action Program investigators, for instance, recommended antibiotics followed by another CT scan 1 month after nodule detection.^{5,6} However, antibiotic use remains controversial. ACCP practice guidelines,

for instance, cite concerns regarding the unlikelihood of clinically meaningful bacterial infections among lung nodules and the potential for antibiotic resistance.⁴

Given the prevalence of incidentally discovered lung nodules and the paucity of available data on the impact of antibiotics, this preliminary study was designed with two goals in mind: first, to quantify any association that may exist between antibiotic use and improvement in the appearance of pulmonary nodules in patients who are not referred for diagnostic biopsy, and second, to determine what factors, if any, influence the decision to prescribe antibiotics in this circumstance. As people with infectious nodules may be more likely to benefit from antibiotics, a subset analysis was performed for patients who manifested symptoms or radiographic findings suggesting active pulmonary infection.

Table 2—Spectrum of Respiratory Symptoms Experienced at Initial Evaluation

Symptom	All Evaluations (%) (N = 143)	Receiving Antibiotics (%) (n = 34)	Not Receiving Antibiotics (%) (n = 109)
Cough	36 (25)	11 (32)	25 (23)
Dyspnea	29 (20)	6 (18)	23 (21)
Sputum production	13 (9)	4 (12)	9 (8)
Wheezing	11 (8)	4 (12)	7 (6)
Night sweats	7 (5)	2 (6)	5 (5)
Fever	2 (1)	1 (3)	1 (1)
Weight loss	2 (1)	0 (0)	2 (2)
Total patients with symptoms ^a	63 (44)	16 (47)	47 (43)

Data are expressed in terms of number of evaluations and the percentage of evaluations within each column.

^aSome patients suffered more than one symptom.

MATERIALS AND METHODS

Subjects

After obtaining approval from the institutional privacy board, medical records were reviewed of outpatients referred to the pulmonary medicine or thoracic surgery services at a cancer center in New York City between January 2003 and December 2004. All referrals were to evaluate pulmonary nodules; patients with an *International Classification of Diseases 9* billing code of “lung tumor or nodule” (793.1) were deemed eligible. A pulmonary nodule was defined as a single radiographically distinct lesion surrounded on all sides by pulmonary parenchyma.

Patients were excluded if they had been referred for immediate biopsy or surgical resection after their initial CT scans, if their nodules were already stable for 2 or more years, if they had only

Table 3—Outcome of Evaluation of Pulmonary Nodules

Outcome	Nodule Numbers (%) (N = 293)
Stable	192 (66)
Resolved	67 (23)
NSCLC	19 (6)
Granuloma	9 (3)
TB	2 (1)
Metastatic cancer	3 (1)
Anthraxis	1 (<1)

Data are expressed in terms of number of nodules and percentage of all nodules. NSCLC = non-small cell lung cancer.

one CT scan performed, or if radiographic abnormalities were 3 cm or more in diameter. This size implies, by definition, a lung mass, and may be evaluated differently.

End Points

The primary end point was the appearance of each nodule on the first follow-up scan. Each was described as being increased or decreased in size, remaining the same size, or resolved. A nodule was considered improved if there was any decrease in size or resolution. A subset analysis was performed for patients with symptoms or radiographic findings suggesting pulmonary infection. Symptoms were prospectively identified as cough, dyspnea, sputum production, wheezing, night sweats, and fever, and must have been present for at least 1 month at the initial clinical evaluation. Radiographic findings included the presence of nodules in clusters,⁷ a tree-in-bud pattern,^{8,9} and bronchiectasis.^{10,11} Nodules were said to have a tree-in-bud character if they were centrilobular and had branching linear structures originating from a single stalk.¹² All nodules were followed until a biopsy was performed or 2 years of radiographic follow-up had been completed.

Data Collection

Once eligibility was established, the following data were acquired from each patient's medical record: (1) demographic information, including name, age, gender, and date of birth; (2) dates of the index CT scan and the initial clinical evaluation; (3) smoking status and number of pack-years; (4) presence or absence of cough, sputum, dyspnea, fever, night sweats, or weight loss for at least 1 month;

Table 4—Appearance of Nodule on First Follow-up CT Scan

Appearance	All Nodules (%) (N = 293)	Receiving Antibiotics (%) (n = 72)	Not Receiving Antibiotics (%) (n = 221)
Increased	11 (4)	2 (3)	9 (4)
Remained the same	198 (67)	46 (64)	152 (69)
Decreased	40 (14)	14 (19)	26 (12)
Resolved	44 (15)	10 (14)	34 (15)
Beneficial response ^a	95%	95%	95%
	CI, 20.8-36.5	CI, 17.6-49	CI, 18.3-36

Data are expressed in terms of number of nodules and percentage within each column. A beneficial result was defined as a decrease in size or resolution in the appearance of the nodule. Percentages and CIs are based on the sum of all nodules within each column.

^aP = .46

(5) any referral for biopsy and the type of biopsy performed; and (6) final diagnosis of each nodule.

Nodules were considered benign if there was no significant radiographic change 2 years from the initial study, the nodules resolved, or an examination of biopsy specimens detected a nonmalignant condition. Nodules were considered malignant based on biopsy results. Biopsy procedures typically included bronchoscopy, percutaneous fine needle aspiration, and surgical resection.

All radiographic data were obtained by one of the investigators (S. M.), a board-certified radiologist blinded to all clinical information. Radiology reports obtained in the course of usual clinical care were not used; many did not include sufficient information or make comparisons with earlier studies. Whenever multiple nodules were present, characteristics of only the three largest were included. The radiologist recorded the size, number, and location of each nodule and quantified characteristics, defined above, prospectively identified as possibly reflecting infection. Additional features of benignity or malignancy, potentially influencing the decision to prescribe antibiotics that were recorded, included nodule size,^{13,14} density,¹⁵ margin appearance,¹⁶ and subpleural location.¹⁷

Statistical Analysis

Patient and nodule characteristics are summarized using descriptive statistics such as frequency and proportion for categorical variables and mean and median for quantitative variables. A nodule was deemed to have a response if it decreased in size or resolved. Response is a nodule-level characteristic, and up to three nodules were evaluated for response for each subject. Thus the response variable is of the clustered binary data form in which nodules are clustered within subjects. The CI for response rate was obtained by calculating a bootstrap standard error in which subjects are sampled with replacement. The association between antibiotic use and nodule response was tested using a χ^2 statistic. As in the CI calculation, we accounted for clustering using a permutation technique. The subjects were stratified by the number of nodules evaluated (ie, one, two, or three). Under the null hypothesis of no association, the antibiotics status could be randomly permuted within each stratum. The χ^2 statistic was computed from the randomly permuted data, and the *P* value was the proportion of times the permuted χ^2 was at least as large as the χ^2 from the original data.

Another question of interest was to identify factors influencing the prescription of antibiotics. The variables that influenced this could be subject-level characteristics (eg, respiratory symptoms) or nodule-level characteristics (eg, size, location). The association between the variables and the binary end point of antibiotic prescription were evaluated using a χ^2 test for categorical variables (eg, location) and the Wilcoxon rank sum test for quantitative variables (eg, size). As described earlier, we accounted for clustering using a permutation technique when the variable of interest was at the nodule level.

RESULTS

Study Population

Among the 114 patients who underwent evaluation during the time period studied, some had additional nodules detected incidentally on follow-up examinations, requiring additional evaluation. Thirteen patients were evaluated twice, six patients three times, and one patient five times. Thus, 143 total evaluations

Table 5—Appearance of Nodules Among Symptomatic Patients on First Follow-up CT Scan

Appearance	All Nodules (%) (n = 129)	Receiving Antibiotics (%) (n = 29)	Not Receiving Antibiotics (%) (n = 100)
Increased	5 (4)	0	5 (5)
Remained the same	84 (65)	17 (59)	67 (67)
Decreased	16 (12)	8 (27)	8 (8)
Resolved	24 (19)	4 (14)	20 (20)
Beneficial response ^a	40 (31) 95%	12 (41) 95%	28 (28) 95%
	CI, 18.9-43.1	CI, 14.8-68	CI, 14.0-42

Sixty-three patients had one or more of the following symptoms for at least 1 month at their initial clinical evaluation: cough, dyspnea, sputum production, wheezing, night sweats, and fever. Data are expressed in terms of number of nodules and percentage within each column. A beneficial result was defined as a decrease in size or resolution in the appearance of the nodule. Percentages and CIs are based on the sum of all nodules within each column.

^a*P* = .44

were performed of 293 nodules. Because some patients were evaluated more than once, all data are presented in terms of number of evaluations unless otherwise stated.

Demographic data are shown in Table 1. Most of the evaluations were performed for women (73%) and ever smokers (68%). The median number of nodules per evaluation was two, and the median nodule diameter was 5 mm. The median time interval from the initial CT scan to the first follow-up study was 109 days. Antibiotics were prescribed to 34 (24%) of 143 evaluations. Fluoroquinolone antibiotics were prescribed for 12 evaluations (8%), macrolides for 16 evaluations (11%), and antituberculous antibiotics for two evaluations (1%). For four evaluations (3%), no antibiotic was specified. Those receiving

Table 6—Appearance on First Follow-up CT Scan of Nodules Among Patients With Radiographic Findings Suggesting Infection

Appearance	All Nodules (%) (n = 114)	Receiving Antibiotics (%) (n = 35)	Not Receiving Antibiotics (%) (n = 79)
Increased	3 (3)	2 (6)	2 (3)
Remained the same	69 (61)	21 (60)	49 (62)
Decreased	20 (18)	6 (17)	13 (16)
Resolved	21 (18)	6 (17)	15 (19)
Beneficial response ^a	41 (36) 95%	12 (34) 95%	28 (35) 95%
	CI, 23.0-47	CI, 10.3-58.3	CI, 19.1-52.7

Sixty-seven patients had CT scans demonstrating nodules in clusters, a tree-in-bud pattern, or bronchiectasis. Data are expressed in terms of number of nodules and percentage within each column. A beneficial result was defined as a decrease in size or resolution in the appearance of the nodule. Percentages and CIs are based on the sum of all nodules within each column.

^a*P* = .7

antibiotics had nodules with slightly larger median diameters (7 mm vs 5 mm, *P* < .01) and underwent their first follow-up CT scan sooner (96 days vs 119 days, *P* < .01) than those who did not. Otherwise, data regarding age, gender, tobacco use, prior malignancy, nodule number, and the prevalence of symptoms were not different between the two groups.

Respiratory symptoms had been present for at least 1 month among 63 (44%) of all evaluations at the initial evaluation. Table 2 shows that cough and dyspnea were most common, occurring among 25% and 20% of all evaluations, respectively. There was no difference in the type or distribution of symptoms between patients who received antibiotics and those who did not.

Nineteen diagnostic biopsies were performed. All other patients were followed for 2 years or until their nodules had resolved. Table 3 shows the final etiology results of all nodules. Most remained stable or resolved and were thought to be benign.

Results After Antibiotics

Table 4 shows the appearance of pulmonary nodules on the first follow-up imaging study. Because some scans showed mixed results within the same patient (ie, one nodule grew while another decreased in size), data are presented as a function of the number of nodules. Although Table 4 shows a trend toward improvement with antibiotics, this was not statistically significant. The percentage of all nodules that improved (ie, decreased in size or resolved) was 33% among patients receiving antibiotics and 27% among those who did not (Table 4) (odds ratio 1.33, 95% CI, 0.55-3.27; *P* = .46). There remained no significant difference accounting for nodule size or the time interval preceding the first follow-up study. Similarly, no statistical difference was seen in the setting of symptoms or radiographic findings that suggested infection. For patients with symptoms, 41% of nodules improved among patients receiving antibiotics and 28% among those who did not (Table 5) (odds ratio, 1.78; 95% CI, 0.42-7.78; *P* = .44). For patients with radiographic findings that suggested infection, the percentage of nodules that improved with and without antibiotics was 34% and 35% respectively (Table 6) (odds ratio, 0.95; 95% CI, 0.25-3.56; *P* = .70).

Determinants of Antibiotic Use

Clinical and radiographic findings potentially influencing the decision to prescribe antibiotics are shown in Tables 7 and 8. Because it is possible that nodules within the same patient may have different characteristics, data in Table 7 are expressed as a function of the number of individual nodules. Data independent of the number of nodules per patient, such as the presence

Table 7—Association of Nodule Characteristics With Antibiotic Use

Characteristic	Receiving Antibiotics (%) (n = 72)	Not Receiving Antibiotics (%) (n = 221)	P Value
Median nodule size, mm	7	5	<.01
Subpleural location (as opposed to parenchymal)	37 (51)	141 (64)	.19
Clusters	31 (43)	58 (26)	.12
Location			.13
Lower lobe	25 (35)	113 (52)	...
Middle lobe	14 (20)	38 (17)	...
Upper lobe	32 (45)	68 (31)	...
Density ^a			.81
Solid	11 (15)	44 (20)	...
Partly solid	31 (44)	89 (41)	...
Nonsolid	29 (41)	84 (39)	...
Margins ^b			.49
Lobulated	49 (69)	130 (60)	...
Smooth	10 (14)	55 (25)	...
Spiculated	6 (8)	12 (6)	...

Data are expressed in terms of number of nodules and percentage within each column.

^aThree nodules were too small for density to be noted.

^bTwenty-six nodules were too small for margin characteristics to be specified.

of respiratory symptoms, are expressed in Table 8 as a function of the number of patient evaluations. Only larger nodule size and bronchiectasis were identified as factors associated with the decision to prescribe antibiotics.

DISCUSSION

Pulmonary nodules are frequent incidental findings on CT scans. Nodules thought to be too small for biopsy or unlikely to be malignant are often referred for serial imaging. Such a strategy is costly, is associated with significant radiation exposure, and causes anxiety in patients who are aware that radiographic abnormalities exist but unaware of their cause. Consequently, it is tempting to believe that a simple and relatively inexpensive modality, such as oral antibiotics, promotes nodule resolution. Supporters of antibiotic use cite their effectiveness against numerous bacterial

Table 8—Association of Nodule or Patient Characteristics With Antibiotic Use

Characteristic	Receiving Antibiotics (%) (n = 34)	Not Receiving Antibiotics (%) (n = 109)	P Value
Any respiratory symptom	16 (46)	47 (44)	.70
Bronchiectasis	17 (50)	33 (30)	.04
Tree-in-bud pattern	9 (26)	18 (17)	.33

Data are presented in terms of number of evaluations and percentage of evaluations within each column. Types of respiratory symptoms are shown in Table 2.

and inflammatory disorders that cause pulmonary nodules. Macrolide antibiotics are known to have antiinflammatory properties independent of their antimicrobial effects and have been used to treat such inflammatory disorders as panbronchiolitis,¹⁸⁻²¹ asthma,^{20,22} bronchiectasis,^{23,24} and cryptogenic organizing pneumonia.²⁵

While this study suggested a trend toward improvement among nodules in the antibiotic group, the finding was not quite sufficient to prove an association. This is consistent with ACCP guidelines published in 2007, which cite concerns that bacterial infections cause a minority of nodules; hence, routine antibiotics would rarely result in improvement and may promote antibiotic resistance.⁴ Furthermore, this study could not find any significant association among patients thought most likely to respond to antibiotics, specifically those manifesting symptoms and radiographic findings indicating infection.

Another study aim was to determine what clinical and radiographic factors, if any, influence the decision to prescribe antibiotics. The results suggest that only larger nodule size and bronchiectasis are associated. Interestingly, symptoms and radiographic features thought indicative of infection were otherwise not associated with this decision. It is not known why prescribing antibiotics was not more closely related to indicators of infection; this may reflect a diversity of opinion among physicians regarding antibiotic use in this setting.

The widespread availability of CT technology implies that finding incidental lung nodules will remain a common occurrence. It is therefore noteworthy that, to our knowledge, no compelling studies to date exist supporting or refuting antibiotic use for nodules thought too small for biopsy, at low risk for malignancy, and/or whose attributes do not suggest any specific cause. Libby et al⁶ reviewed patients who underwent baseline and surveillance screening CT scans through the Early Lung Cancer Action Program, finding 80 patients who were given antibiotics by the investigators. All were asymptomatic, and 41 (51%) showed improvement on follow-up imaging examinations. However, conclusions were limited by the absence of any control group and the lack of any standard indication for prescribing antibiotics (some were prescribed for small infiltrates).

Some limitations exist in our study. It is retrospective in design and not randomized, rendering it susceptible to problems inherent to studies of this type, including confounding by indication. For instance, patients with nodules who are treated with antibiotics might be inherently different from those who did not receive antibiotics in ways that were not observed. The population studied comes from a single, urban medical center.

While inclusion criteria were limited to specific clinical and radiographic findings, no systematic method existed to determine the antibiotic employed. Patients given antibiotics received their first follow-up CT scans sooner, but any bias resulting from this difference would favor a change in the nonantibiotic group (ie, greater time to follow-up CT scan allows more time for observable changes to occur). Moreover, this time discrepancy was accounted for in the statistical analysis.

Finally, the suggestion that more nodules had improved among patients receiving antibiotics, while not statistically significant, indicates this study may not have been adequately powered. It was not possible to calculate an ideal sample size before undertaking this study because, to our knowledge, no objective data in the literature existed with which to do so. Subsequently, a *post hoc* analysis was performed, based on the data described herein, concluding that at least 1,000 evaluations would have been required to detect a 10% improvement in the antibiotic group—an end point that seemed reasonable from these preliminary data. This number may serve as a guide for future investigators studying the role of antibiotics in pulmonary nodules.

To our knowledge, this is the first systematic analysis of antibiotic use in treating pulmonary nodules. While a strong trend toward nodule improvement was seen in patients taking antibiotics, no firm association was proven; therefore, this study cannot support the widespread use of antibiotics empirically. As technology continues to improve and render ever more accurate images, this study is timely and may give pause to clinicians tempted to prescribe antibiotics. It is hoped that it will provide an impetus for designing larger prospective trials to clarify the role of antibiotics in the management of lung nodules.

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Contributors: *Dr Khokhar:* is a postdoctoral fellow who was involved in all steps of this research project, including forming the hypothesis, designing analytic strategies, acquiring data, checking data quality, and writing the manuscript.

Dr Mironov: is a board-certified radiologist who personally reviewed all CT scans associated with this study. She was blinded to all other clinical information.

Dr Seshan: is a biostatistician who participated in the data collection and analysis.

Dr Stover: oversaw the forming of the hypothesis and specific aims, as well as checking data quality.

Dr Khirbat: is a postdoctoral fellow who was involved in forming the hypothesis, acquiring the data, and disseminating results through abstracts and national meetings.

Dr Feinstein: was the senior investigator of this project and was involved in every step of its development, including forming the hypothesis and specific aims, checking data quality, assessing and reviewing the data, and overseeing the dissemination of the data in abstracts, national meetings, and publications.

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REFERENCES

1. Henschke CI, Yankelevitz DF, Libby DM, Pasmantier MW, Smith JP, Miettinen OS; International Early Lung Cancer Action Program Investigators. Survival of patients with stage I lung cancer detected on CT screening. *N Engl J Med*. 2006; 355(17):1763-1771.
2. Swensen SJ, Jett JR, Hartman TE, et al. CT screening for lung cancer: five-year prospective experience. *Radiology*. 2005;235(1):259-265.
3. Ost D, Fein AM, Feinsilver SH. Clinical practice. The solitary pulmonary nodule. *N Engl J Med*. 2003;348(25):2535-2542.
4. Gould MK, Fletcher J, Iannettoni MD, et al; American College of Chest Physicians. Evaluation of patients with pulmonary nodules: when is it lung cancer? ACCP evidence-based clinical practice guidelines (2nd edition). *Chest*. 2007;132(3 Suppl): 108S-130S.
5. Henschke CI, McCauley DI, Yankelevitz DF, et al. Early Lung Cancer Action Project: overall design and findings from baseline screening. *Lancet*. 1999;354(9173):99-105.
6. Libby DM, Wu N, Lee IJ, et al. CT screening for lung cancer: the value of short-term CT follow-up. *Chest*. 2006;129(4): 1039-1042.
7. Heo JN, Choi YW, Jeon SC, Park CK. Pulmonary tuberculosis: another disease showing clusters of small nodules. *AJR Am J Roentgenol*. 2005;184(2):639-642.
8. Eisenhuber E. The tree-in-bud sign. *Radiology*. 2002;222(3): 771-772.
9. Rossi SE, Franquet T, Volpacchio M, Giménez A, Aguilar G. Tree-in-bud pattern at thin-section CT of the lungs: radiologic-pathologic overview. *Radiographics*. 2005;25(3):789-801.
10. Ferrara I, Cappabianca S, Brunese L, et al. HRCT in detection of pulmonary infections from nontuberculous mycobacteria: personal experience. *Radiol Med (Torino)*. 2009;114(3): 376-389.
11. Tanaka D, Niwatsukino H, Oyama T, Nakajo M. Progressing features of atypical mycobacterial infection in the lung on conventional and high resolution CT (HRCT) images. *Radiat Med*. 2001;19(5):237-245.
12. Li Ng Y, Hwang D, Patsios D, Weisbrod G. Tree-in-bud pattern on thoracic CT due to pulmonary intravascular metastases from pancreatic adenocarcinoma. *J Thorac Imaging*. 2009;24(2):150-151.
13. Gould MK, Ananth L, Barnett PG; Veterans Affairs SNAP Cooperative Study Group. A clinical model to estimate the pretest probability of lung cancer in patients with solitary pulmonary nodules. *Chest*. 2007;131(2):383-388.
14. McWilliams A, Mayo J. Computed tomography-detected noncalcified pulmonary nodules: a review of evidence for significance and management. *Proc Am Thorac Soc*. 2008;5(9): 900-904.
15. Swensen SJ, Viggiano RW, Midthun DE, et al. Lung nodule enhancement at CT: multicenter study. *Radiology*. 2000; 214(1):73-80.
16. Wahidi MM, Govert JA, Goudar RK, Gould MK, McCrory DC; American College of Chest Physicians. Evidence for the treatment of patients with pulmonary nodules: when is it lung cancer? ACCP evidence-based clinical practice guidelines (2nd edition). *Chest*. 2007;132(3 Suppl):94S-107S.
17. Takashima S, Sone S, Li F, et al. Small solitary pulmonary nodules (< or = 1 cm) detected at population-based CT screening

- for lung cancer: reliable high-resolution CT features of benign lesions. *AJR Am J Roentgenol*. 2003;180(4):955-964.
18. Kudoh S. Applying lessons learned in the treatment of diffuse panbronchiolitis to other chronic inflammatory diseases. *Am J Med*. 2004;117(Suppl 9A):12S-19S.
 19. Rubin BK. Immunomodulatory properties of macrolides: overview and historical perspective. *Am J Med*. 2004;117(Suppl 9A):2S-4S.
 20. Tamaoki J, Kadota J, Takizawa H. Clinical implications of the immunomodulatory effects of macrolides. *Am J Med*. 2004;117(Suppl 9A):5S-11S.
 21. Wolter J, Seeney S, Bell S, Bowler S, Masel P, McCormack J. Effect of long term treatment with azithromycin on disease parameters in cystic fibrosis: a randomised trial. *Thorax*. 2002;57(3):212-216.
 22. Garey KW, Alwani A, Danziger LH, Rubinstein I. Tissue reparative effects of macrolide antibiotics in chronic inflammatory sinopulmonary diseases. *Chest*. 2003;123(1):261-265.
 23. King P. Is there a role for inhaled corticosteroids and macrolide therapy in bronchiectasis? *Drugs*. 2007;67(7):965-974.
 24. Tsang KW, Ho PI, Chan KN, et al. A pilot study of low-dose erythromycin in bronchiectasis. *Eur Respir J*. 1999;13(2):361-364.
 25. Stover DE, Mangino D. Macrolides: a treatment alternative for bronchiolitis obliterans organizing pneumonia? *Chest*. 2005;128(5):3611-3617.