2198. Weak Interobserver Reliability in the Clinical Diagnosis of Pneumonia Among Infectious Disease Trained Physicians

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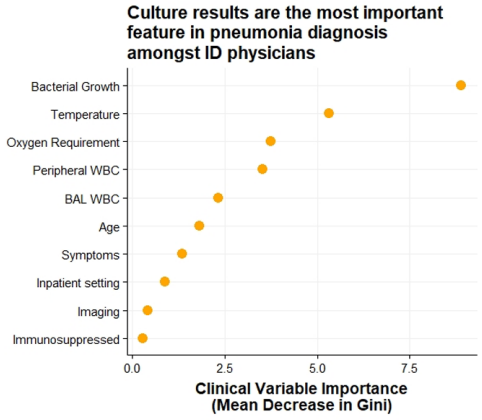
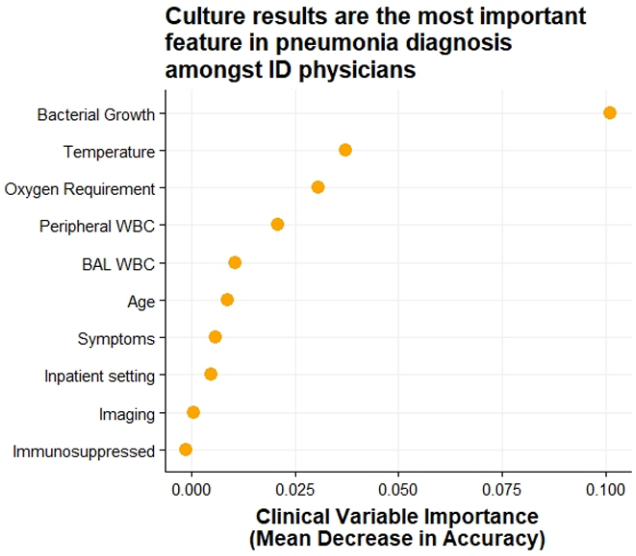
Background. Pneumonia remains a common global cause of death. Varied definitions of pneumonia rely on clinical features, imaging, and microbiological data. The Center for Diseases Control/National Healthcare Surveillance Network (CDC/NHSN) definition is used to study population-level trends. Prior studies have revealed discordance in components of the definition, yet reliability of overall clinical diagnosis has not been evaluated, nor has it been compared with the surveillance definitions. This study was designed to determine the overall concordance in the diagnosis of pneumonia by Infectious Diseases (ID) clinicians and the agreement between this and the surveillance definition. We then set out to determine which clinical features were weighted most heavily in provider decision-making.

Methods. Using an iterative approach with input from ID and Pulmonary Medicine physicians, we designed and refined an adjudication tool for diagnosis of pneumonia that consolidates clinical features, laboratory data, and imaging. Cases were analyzed by strict CDC/NHSN surveillance criteria and adjudicated independently by ID-trained physicians based on overall clinical opinion. Kappa coefficient (κ) was used to determine diagnostic reliability, and a random forest model was used to identify clinical factors most heavily weighted by physicians.

Results. Twenty-eight cases were adjudicated by three ID-trained physicians. Overall, interrater agreement was low (κ = 0.438). In comparing providers' clinical adjudication with CDC/NHSN criteria, agreement was even worse (κ range 0.125 to 0.378). Among specific clinical features, positive culture growth strongly informed clinician diagnosis of pneumonia, while chest imaging did not play a significant role.

Conclusion. Overall agreement in the clinical diagnosis of pneumonia is poor, even among ID-trained physicians. Culture results more strongly inform clinician decision-making than does chest imaging. The surveillance definition used by the CDC/NHSN has only weak agreement with in-practice clinical assessment. These results underscore the need for more precise diagnostic tools in cases of suspected pneumonia.





Disclosures. **All authors:** No reported disclosures.

2199. The Etiology of Community-Acquired Pneumonia with Attention to the Role of Normal Respiratory Flora

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Background. Intensive studies have failed to identify an etiologic agent in >50% of patients (patients) who are hospitalized for community-acquired pneumonia (CAP). Gram stain and culture of sputum samples frequently yield "normal respiratory flora" (NRF). We hypothesized that careful study might (1) increase the yield of recognized pathogens; and (2) show, in some patients, an etiologic role for NRF.

Methods. We studied a convenience sample of adults hospitalized for CAP at a VA Medical Center if they met four criteria: (1) clinical syndrome consistent with pneumonia; (2) newly recognized pulmonary infiltrate; (3) sputum with > 10 WBC per epithelial cell; and (4) < 18 hours antibiotic treatment. For quantification of bacteria, sputum was liquefied in 2% N-acetyl cysteine and diluted serially. Other studies in nearly all patients included blood cultures, urine for pneumococcal (Spn) and *Legionella* antigen, procalcitonin, B-natriuretic protein and PCR for 13 respiratory viruses, *Mycoplasma* and *Chlamydia*. >10^6 bacteria/mL and a consistent Gram stain indicated a bacterial cause, positive viral PCR indicated a viral cause, and both indicated coinfection.

Results. 119 patients met study criteria. Recognized bacterial pathogens alone were identified in 47 (40%) cases led by Spn 17 (14%), *Haemophilus* 17 (14%) and *S. aureus* 6 (5%). A virus alone was identified in 17 (15%) and coinfection in 11 (9%). We applied these same criteria for NRF. NRF alone were found in 22 (19%) patients with *S. mitis* predominating. NRF and a respiratory virus were coinfecting in 10 (8%) patients. In total, with the inclusion of NRF, an etiologic agent was found in 95% of patients.

Conclusion. Our high yield is attributable to selection criteria. With a good-quality sputum and absent prolonged antibiotics, a bacterial cause for CAP was found in 59% of patients, a viral cause in 15%, and coinfection in 17%. Bacterial CAP due to recognized pathogen follows microaspiration of colonizing bacteria from the upper airways. Aspiration of a sufficient inoculum of so-called NRF, especially in older adults or those with damaged clearance mechanisms, might well do the same. Careful microbiologic study of patients who are able to provide a valid sputum sample before prolonged antibiotics enables a microbiologic diagnosis in nearly all cases and shows a potential etiologic role for NRF in about 20%.

Table 1. Etiology of Community Acquired Pneumonia

Etiologic agent by Gram stain and quantitative culture	Percentage of total cases
Recognized bacterial pathogen	40%
Non-recognized bacterial pathogen	19%
Viral pathogen alone	15%
Recognized bacterial pathogen and viral coinfection	9%
Non-recognized bacterial pathogen and viral coinfection	8%
Uninfected	3%
Unknown	5%
Total	**100%**

Disclosures. **All authors:** No reported disclosures.

2200. Cost-effectiveness of Ceftolozane/Tazobactam for Treating Ventilated Nosocomial Bacterial Pneumonia

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Background. Ventilated, hospital-acquired and ventilator-associated bacterial pneumonia (vHABP/VABP) are associated with high rates of antibiotic resistance and high morbidity and mortality in hospitalized patients. Ceftolozane/tazobactam (C/T) has shown non-inferiority to meropenem for treating HABP/VABP in a Phase III trial, ASPECT-NP. This study evaluates cost-effectiveness of C/T against meropenem in treating HABP/VABP.

Methods. We developed a model consisting of a short-term decision tree (reflecting the in-hospital period) followed by a long-term Markov structure (capturing lifetime costs and outcomes). Patient characteristics and clinical efficacy were informed by subjects in ASPECT-NP who received any dose of study drugs. Susceptibility was based on the Program to Assess C/T Susceptibility surveillance database. Second-line and salvage treatment were added to resemble real-world treatment patterns and used to calculate overall clinical cure and mortality rates based on results from a network meta-analysis. We analyzed two clinical scenarios: (1)"confirmed treatment' in which C/T or meropenem is used after pathogen susceptibility is known; (2) 'initial treatment' of high-risk patients before susceptibility is known. Model outcomes include, percentage clinically cured, short-term mortality, direct medical costs, quality-adjusted

life years (QALYs), and incremental cost-effectiveness ratios. Sensitivity analyses (SAs) were conducted to test the robustness of results.

Results. In the confirmed treatment setting, C/T had a higher cure rate (5.0 percentage points, the same below), lower short-term mortality (−5.1%), cost more ($2,728), and yielded higher lifetime QALYs (0.61) than meropenem ($4,472/QALY gained). In the initial treatment setting, C/T sustained a better clinical performance (9.5% more cure, −6.8% mortality, 1.16 more QALYs), yet cost less than meropenem (−$5,662) due to better susceptibility. The response and mortality rates from ASPECT-NP had the greatest impact on results. SAs showed that the result of C/T being cost-effective over meropenem was generally robust.

Conclusion. The results indicate that, compared with meropenem, C/T could be a cost-effective option for patients with vHABP/VABP in the US setting.

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2201. Cost of Antimicrobial Use Against Upper Respiratory Infection in Japan

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Background. Antibiotics are often inappropriately prescribed for treating upper respiratory infection (URI) patients in ambulatory care settings. In Japan, a previous study estimated physicians prescribed antibiotics in about 30% of URI cases. However, trends of prescription behavior and additional costs of inappropriate antibiotic use in URI cases are still not clear in Japan. The present study's main objective was to clarify the amount of additional cost owing to inappropriate antibiotic prescription for URI, and the recent trend.

Methods. We conducted a retrospective observational survey using longitudinal claims data spanning 2013–2016, obtained from the Japan Medical Data Center Co., Ltd. (JMDC) Claims Database, which contains anonymous claim data on 5.1 million (for 2013–2016) corporate employees covered by the employees' health insurance plan (Social insurance), and their family members <65 years old. Six physicians specialized in infectious disease assessed the appropriateness of antibiotic prescription based on the ICD-10 code in the database. The total additional cost of antibiotic prescription for URI at the national level was estimated by weighting corresponds to the age-structured population data, from the healthcare payer perspective. Costs of treatment for adverse events and of antimicrobial resistance caused by inappropriate antibiotic prescription were not taken into consideration.

Results. The total annual cost of antibiotic prescription for URI was estimated at US$423.6 (95% confidence interval: 416.8–430.5) million in 2013, $340.9 (335.7–346.2) million in 2014, $349.9 (344.5–355.3) million in 2015, and $297.1 (292.4–301.9) million in 2016.

Conclusion. Although a decreasing trend was observed, the annual cost of antibiotic prescription for URI potentially imposes a substantial economic burden in Japan.

Year	2013	2014	2015	2016
0-4	300045 (5.73)	349827 (6.71)	364043 (7.27)	378095 (7.62)
5-9	186265 (3.47)	199763 (3.76)	190513 (3.58)	183465 (3.46)
10-14	178937 (3.09)	195988 (3.43)	185914 (3.31)	178224 (3.23)
15-19	181308 (3.0)	232657 (3.87)	229207 (3.79)	229102 (3.79)
20-24	206669 (3.33)	301604 (4.86)	310845 (5.10)	319438 (5.19)
25-29	234889 (3.42)	301904 (4.52)	301886 (4.62)	303908 (4.75)
30-34	254486 (3.34)	304273 (4.08)	298905 (4.04)	297681 (4.10)
35-39	279942 (3.09)	319855 (3.69)	309508 (3.68)	302943 (3.73)
40-44	266656 (2.76)	299446 (3.06)	288814 (2.93)	281933 (2.90)
45-49	219357 (2.61)	242943 (2.82)	233439 (2.66)	227467 (2.45)
50-54	174821 (2.26)	198847 (2.55)	190321 (2.37)	184999 (2.34)
55-59	129055 (1.67)	172490 (2.25)	164890 (2.17)	159649 (2.12)
60-64	107417 (1.11)	146718 (1.63)	142367 (1.66)	138287 (1.70)
Total	2719847 (2.85)	3266315 (3.47)	3210652 (3.44)	3185191 (3.45)

Table 1. Number of enrollees in each age group*

*Numbers in brackets represent the proportion of enrollees in total number of Japanese populations in each age group

Year	2013	2014	2015	2016
0-4	22.45 (22.37-22.52)	21.59 (21.52-21.66)	20.14 (20.07-20.21)	18.87 (18.80-18.94)
5-9	30.92 (30.79-31.05)	30.37 (30.25-30.50)	28.32 (28.20-28.44)	26.75 (26.63-26.87)
10-14	36.88 (36.69-37.08)	35.95 (35.76-36.13)	34.56 (34.39-34.74)	33.04 (32.86-33.22)
15-19	43.29 (43.0-43.58)	42.02 (41.75-42.30)	41.71 (41.45-41.97)	37.87 (37.63-38.12)
20-24	44.05 (43.74-44.36)	42.72 (42.42-43.01)	43.61 (43.32-43.91)	40.49 (40.21-40.78)
25-29	42.51 (42.24-42.78)	41.68 (41.42-41.94)	42.09 (41.84-42.35)	39.99 (39.73-40.24)
30-34	42.74 (42.51-42.96)	42.01 (41.79-42.23)	41.52 (41.30-41.74)	39.80 (39.58-40.02)
35-39	42.82 (42.61-43.04)	42.09 (41.88-42.30)	41.45 (41.24-41.66)	39.98 (39.77-40.19)
40-44	41.6 (41.37-41.82)	40.95 (40.74-41.17)	40.46 (40.26-40.67)	39.04 (38.83-39.25)
45-49	39.10 (38.85-39.35)	38.16 (37.93-38.40)	38.40 (38.17-38.62)	36.87 (36.65-37.10)
50-54	36.75 (36.49-37.01)	36.31 (36.06-36.56)	36.09 (35.85-36.33)	34.79 (34.55-35.02)
55-59	35.45 (35.16-35.74)	34.88 (34.60-35.15)	35.04 (34.78-35.30)	33.45 (33.20-33.71)
60-64	33.62 (33.30-33.94)	33.06 (32.74-33.38)	33.27 (32.96-33.58)	31.71 (31.40-32.02)
Total	32.35 (32.30-32.40)	31.62 (31.57-31.67)	30.96 (30.91-31.01)	29.33 (29.28-29.37)

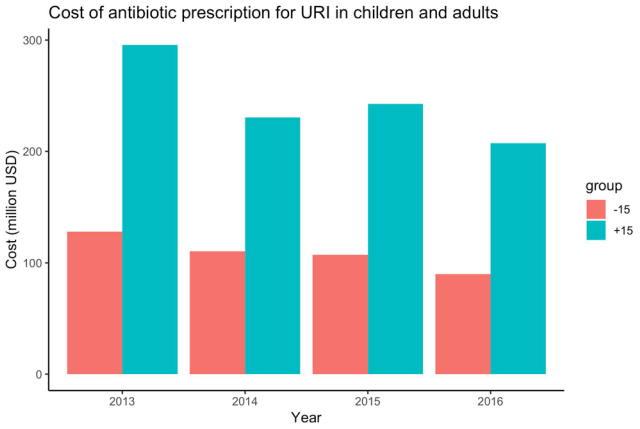
Table 2. Estimated proportion of antibiotic prescription against URI in ambulatory care*

*Numbers are represented by percentage. Numbers in brackets represent 95% confidence interval.

Year	2013	2014	2015	2016
0-4	40.3 (39.9-40.7)	32.7 (32.4-33.0)	27.2 (26.9-27.5)	22.1 (21.8-22.3)
5-9	56.6 (55.9-57.3)	50.1 (49.5-50.7)	51.1 (50.5-51.8)	43.4 (42.8-43.9)
10-14	31.2 (30.7-31.7)	27.7 (27.3-28.1)	29.0 (28.6-29.4)	24.4 (24.0-24.7)
15-19	19.5 (19.1-19.8)	14.6 (14.4-14.8)	16.1 (15.8-16.4)	14.0 (13.8-14.3)
20-24	17.2 (16.9-17.5)	11.4 (11.2-11.6)	11.1 (11.0-11.3)	9.5 (9.3-9.6)
25-29	22.4 (22.0-22.7)	16.1 (15.8-16.4)	15.5 (15.3-15.8)	12.6 (12.4-12.8)
30-34	31.2 (30.8-31.7)	23.9 (23.6-24.2)	23.9 (23.5-24.2)	19.8 (19.5-20.1)
35-39	38.0 (37.4-38.5)	29.9 (29.5-30.3)	29.6 (29.2-30.0)	23.7 (23.4-24.1)
40-44	39.7 (39.1-40.2)	34.9 (34.4-35.4)	37.6 (37.1-38.1)	30.5 (30.1-30.9)
45-49	31.9 (31.3-32.4)	28.4 (28.0-28.9)	31.8 (31.3-32.3)	30.3 (29.8-30.8)
50-54	29.4 (28.8-29.9)	26.2 (25.7-26.7)	30.0 (29.5-30.6)	26.2 (25.7-26.7)
55-59	31.1 (30.4-31.8)	23.0 (22.5-23.4)	25.3 (24.8-25.8)	23.0 (22.6-23.5)
60-64	35.4 (34.5-36.3)	22.0 (21.5-22.6)	21.7 (21.2-22.2)	17.7 (17.3-18.2)
Total	423.6 (416.8-430.5)	340.9 (335.7-346.2)	349.9 (344.5-355.3)	297.1 (292.4-301.9)

Table 3. Estimated additional cost of antibiotic use against URI in ambulatory care (unit = million USD)*

*Numbers in brackets represent 95% confidence interval.



Disclosures. **All authors:** No reported disclosures.

2202. Validation of a Rabbit Model of *Pseudomonas aeruginosa* Acute Pneumonia

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Background. Severity and antimicrobial resistance of *P. aeruginosa* (PA) hospital-acquired pneumonia led the FDA to encourage the development of animal models for preclinical evaluation of new therapeutic strategies. We present here the validation of a rabbit model of PA acute pneumonia.

Methods. Rabbits were infected by endotracheal instillation of 1.8 mL of a standardized inoculum containing 9×10^7 CFU of PA clinical strain 6206 (predetermined 100% lethal dose). The natural history of the disease was described by the following parameters evaluated at 3, 4, 5, 6, 10 hours post-infection (hpi) and at the time of spontaneous death (6 rabbits/group): lung-to-body weight ratio (LW/BW), pulmonary, splenic and renal bacterial counts, pulmonary histology and blood markers (blood cell counts, blood gas and IL-8). Three groups of 12 rabbits were then treated with saline (controls), tobramycin or meropenem at doses determined by PK/PD analysis to confirm the efficacy of a human-equivalent dosing regimen.

Results. PA strain 6,206 caused fatal pneumonia in 13–23 hours by acute respiratory distress syndrome (pulmonary edema and necrosis with LW/BW > 10, pO_2 <40 mmHg) and/or sepsis (hyperlactatemia, hypoglycemia, cytopenias). LW/BW and pulmonary bacterial counts increased significantly over time. The splenic and renal bacterial spread was constant after 6 hpi. Hypoxemia <60 mmHg appeared at 5 hpi for 4/6 rabbits, associated with elevated plasma IL-8 concentration, massive neutrophilic influx into the airspace, lung necrosis, hemorrhage, and pulmonary edema formation. Consequently, 5 hpi appeared as the most appropriate time to trigger a therapeutic intervention. Meropenem (80 mg/kg/q2h) or tobramycin (1 injection of 2.5 mg/kg, then saline/q2h) showed superiority over saline, with a mortality rate of 33% and 17% *vs.* 100%, and an LW/BW ratio of 8.53 and 8.54 *vs.* 13.9, respectively. Tobramycin was less effective than meropenem in clearing bacteria, with, respectively, 1 and 9 out of 12 rabbits having sterile samples.

Conclusion. This rabbit model of PA acute pneumonia is a reliable evaluation tool for new therapeutic strategies. Our study also provides guidance for the