Role of Atypical Bacteria in Hospitalized Patients With Nursing Home-Acquired Pneumonia

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ABSTRACT

Background: Nursing home-acquired pneumonia (NHAP) has been identified as one of the leading causes of mortality and hospitalization for long-term care residents. However, current and previous pneumonia guidelines differ on the appropriate management of NHAP in hospitalized patients, specifically in regard to the role of atypical bacteria such as *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, and *Legionella*.

Objectives: The purpose of this review is to evaluate clinical trials conducted in hospitalized patients with NHAP to determine the prevalence of atypical bacteria and thus the role for empiric antibiotic coverage of these pathogens in NHAP.

Methods: Comprehensive MEDLINE (1966–April 2016) and Embase (1980–April 2016) searches were performed using the terms “atypical bacteria”, “atypical pneumonia”, “nursing-home acquired pneumonia”, “pneumonia”, “elderly”, “nursing homes”, and “long term care”. Additional articles were retrieved from the review of references cited in the collected studies. Thirteen published clinical trials were identified.

Results: In the majority of studies, atypical bacteria were infrequently identified in patients hospitalized with NHAP. However, when an active community-acquired pneumonia (CAP) cohort was available, the rate of atypical bacteria between NHAP and CAP study arms was similar. Only 3 studies in this review adhered to recommended strategies for investigating atypical bacteria; in 2 of these studies, *C. pneumoniae* was the most common pathogen identified in NHAP cohorts.

Conclusion: Although atypical bacteria were uncommon in most NHAP studies in this review, suboptimal microbial investigations were commonly performed. To accurately describe the role of atypical bacteria in NHAP, more studies using validated diagnostic tests are needed.

Key Words—atypical bacteria, nursing home, pneumonia

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Nursing home-acquired pneumonia (NHAP) has been identified as one of the leading causes of mortality and hospitalization for long-term care residents.¹⁻⁴ Yet, the microbial etiology of NHAP is still debated, and a guideline dedicated solely to its management is lacking. In previous community-acquired pneumonia (CAP) guidelines from the American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA), the recommended treatment of NHAP included the provision of atypical bacteria coverage in an antibiotic

strategy similar to that of CAP.⁵⁻⁷ With the release of the 2005 hospital-acquired pneumonia (HAP) and healthcare-associated pneumonia (HCAP) guideline by the ATS and IDSA, NHAP was reclassified as a nosocomial infection under the umbrella term HCAP, and recommendations were focused on the empiric treatment of multidrug resistant (MDR) organisms such as *Pseudomonas* and methicillin-resistant *Staphylococcus aureus* (MRSA).^{8,9} The support for the presence of MDR organisms in NHAP, however, was largely based on the results of 2 cohort studies

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of nursing home residents with pneumonia severe enough to require mechanical ventilation and intensive care.^{10,11} In recent years, the definition and microbial etiology of HCAP have come into question with widespread adherence to the treatment of NHAP as HCAP lacking in the United States and elsewhere.^{12,13} Several countries outside of the United States, in fact, did not adopt the HCAP classification for NHAP.¹⁴⁻¹⁷ In Canada and the United Kingdom, current guidelines endorse NHAP as a form of CAP with emphasis on coverage for atypical bacteria.¹⁴⁻¹⁶ On the other hand, in 2011 Japan created an entirely new pneumonia category—nursing and healthcare-associated pneumonia (NHCAP)—to improve the care of elderly pneumonia patients, who were often classified according to earlier Japanese guidelines as having both CAP and HAP.¹⁷ In July 2016, more than 10 years after the HCAP classification was introduced, the IDSA and ATS revised the HAP guideline and removed the concept of HCAP, claiming the rationale for its previous inclusion as a nosocomial infection is no longer justified based on increasing evidence.¹⁸ However, HCAP (and thus NHAP) “could” make its return to the “upcoming” CAP guideline, according to the 2016 HAP guideline authors.¹⁸ With the growing debate over the proper classification of NHAP and the uncertainty surrounding its microbial etiology, the purpose of this review is to evaluate clinical trials conducted in hospitalized patients with NHAP to determine the prevalence of atypical bacteria and thus the role for empiric antibiotic coverage of *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, and *Legionella* in NHAP.

METHODS

Search Strategy

Comprehensive MEDLINE (1966–April 2016) and Embase (1980–April 2016) searches were performed using the terms “atypical bacteria”, “atypical pneumonia”, “nursing-home acquired pneumonia”, “pneumonia”, “elderly”, “nursing homes”, and “long term care”. Additional articles were retrieved from the review of references cited in the collected studies.

Inclusion and Exclusion Criteria

All results were limited to English-language studies conducted with nursing home residents who had pneumonia and were admitted to the hospital. Studies not performing atypical bacteria investigations or lacking data on atypical bacteria were excluded. A review of the microbial etiology of NHAP based on

published trials from 1978 to 1994 has been previously summarized, and thus studies published prior to 1995 were also excluded from this review.¹⁹

RESULTS

A total of 13 published trials on the microbial etiology of NHAP were selected for review. The included studies were published between 2001 and 2015 and conducted across several countries.

Studies Supporting the Role of Atypical Bacteria in NHAP

The 2 studies demonstrating the largest role of atypical bacteria in NHAP were published by Japanese investigators, Maruyama et al, in 2008 and 2010 as shown in Table 1.²⁰⁻²² In their 2008 prospective, comparative study of patients hospitalized with NHAP or late-onset HAP between June 2004 and May 2005, *C. pneumoniae* was found to be the most common bacterial pathogen in patients with NHAP, occurring in 48% of patients with confirmed microbial etiologies.²⁰ In 2010, Maruyama et al published a similar prospective study comparing the bacterial etiology among patients 85 years of age and older with CAP and NHAP admitted to the same hospital and during the same study period as their previously published study.²² Similar to the 2008 study, just over a 100 patients were enrolled, and again *C. pneumoniae* was found to be the most frequent pathogen among NHAP patients. The frequency of *C. pneumoniae* and *M. pneumoniae* among all NHAP patients was not found to be statistically different than the frequency observed in the comparator CAP cohort ($p = .3162$, $p > .9999$, respectively).²²

In another prospective study, Lim et al²³ compared the etiology of NHAP and CAP patients admitted to a British hospital between October 1998 and late March 2000. In this study, 40 NHAP patients were enrolled, and microbiological etiology was established in 22 patients. Atypical pathogens were detected in 4 of the 22 etiology-confirmed NHAP patients (18%), and all 4 cases were *C. pneumoniae*.^{23,24} This is in comparison to 9 of the 44 CAP patients (20%) who also had confirmed atypical bacteria (p values not available). In a large, prospective study of 1,193 patients between January 2004 and June 2005, Hong Kong investigators Lui and colleagues²⁵ evaluated the role of atypical pathogens in hospitalized patients with CAP, of whom 22.6% (270 patients) were nursing home residents. Atypical bacteria were identified in 28.6% of all patients with

Table 1. Atypical bacteria in nursing home–acquired pneumonia studies

Study [ref]	Study features			Causative pathogens ^b			
	Year ^a	Country	Prospective design	No. with NHAP	No. with confirmed microbial etiology for NHAP	Location of care	<i>Chlamydia pneumoniae</i> <i>Mycoplasma pneumoniae</i> <i>Legionella</i>
Koh et al [32]	2015	Korea	No	58	35	Hospital (ICU; NR)	NR 6 (10.3%) 0
Ma et al [27-28]	2013	China	Yes	108 ^c	74 ^c	Hospital	3 (4.1%) 6 (8.1%) 0
Ewig et al [29-31]	2012	Germany	Yes	518	117	Hospital	NR 1 (0.9%) 13 (11.1%)
Ma et al [26]	2012	China	Yes	116	34	Hospital	Serological tests positive in 2 of the 488 patients with CAP and NHAP.
Miyashita et al [35]	2012	Japan	No	172	NR	Hospital (ICU; NR)	5 0 2
Umeki et al [34]	2011	Japan	No	46	NR	Hospital (ICU; NR)	0 1 1
Maruyama et al [22]	2010	Japan	Yes	54	37	Hospital (ICU; NR)	20 (54.1%) 6 (16.2%) 0
Polverino et al [33]	2010	Spain	Yes	150	57	Hospital (ICU; 20)	2 (3.5%) 2 (3.5%) 3 (5.2%)
Lui et al [25]	2009	China	Yes	270	82	Hospital (ICU; NR)	NR specifically for patients with NHAP (see text).
Maruyama et al [20-21]	2008	Japan	Yes	75	54	Hospital (ICU; 6)	26 (48.1%) 7 (13.0%) 0
El-Solh et al [11]	2002	United States	Yes	52	20	ICU	0 0 1 (5.0%)
El-Solh et al [10]	2001	United States	Yes	47	NR	ICU	0 NR 0
Lim et al [23-24]	2001	United Kingdom	Yes	40	22	Hospital (ICU; 0)	4 (18.2%) NR 0

Note: ICU = intensive care unit; NHAP = nursing home–acquired pneumonia; NHCAP = nursing and healthcare–associated pneumonia; NR = not reported.

^a Year published.

^b Number (percent) of patients with confirmed atypical pathogens out of NHAP patients with confirmed microbial etiologies.

^c Number of NHAP episodes.

confirmed microbial etiologies, and *M. pneumoniae* was the most common pathogen ($n = 78$) followed by *C. pneumoniae* ($n = 55$), *Coxiella burnetii* ($n = 2$), and *L. pneumophila* ($n = 1$). Although the frequency of atypical bacteria in NHAP patients alone was not provided, the majority of atypical pathogens were detected in patients over the age of 65 years (63.4%), with more than 16% of these patients being nursing home residents.²⁵

Studies Suggesting a Small Role of Atypical Bacteria in NHAP

In contrast to the Maruyama et al studies, the majority of studies in this review report a small role of atypical pathogens in NHAP. In a prospective cohort study conducted at a Chinese hospital from October 2009 to September 2010, Ma et al²⁶ sought to compare the microbial etiology of patients 65 years of age or older admitted with CAP (372 patients) and NHAP (116 patients). Of all 488 patients enrolled, 475 (97.3%) had microbiological investigations completed within 48 hours of hospital admission, but only 2 of these patients met the diagnostic criteria for atypical bacteria. In a later publication, Ma et al sought to better define the role of atypical pathogens in NHAP by performing a subgroup analysis of a study of nursing home residents with influenza-like illness.^{27,28} Ninety hospitalized patients with a total of 108 episodes of NHAP were included in the analysis. A causative pathogen was identified in 74 (68.5%) of the 108 NHAP episodes, and atypical bacteria were present in 11 episodes (10.2%). Bacterial findings of *M. pneumoniae* and *C. pneumoniae* were most common, followed by *Chlamydophila psittaci* and *Coxiella burnetii*; no cases of *Legionella* were found.^{27,28}

The largest study in this review is a prospective, comparative study conducted by Ewig et al²⁹ from January 2002 to June 2009 of the clinical characteristics and microbial etiology of patients age 65 years and older who were hospitalized with CAP or NHAP. Microbial data for this study were obtained from a large, multicenter German database known as the Competence Network for Community-acquired pneumonia (CAPNETZ). From this 15-center database, Ewig and colleagues found atypical pathogens to be relatively uncommon in the NHAP cohort.²⁹⁻³¹ As seen in **Table 1**, *Legionella* was the most frequent atypical pathogen among NHAP patients with confirmed etiologies, occurring in 11% of patients as compared to 14.1% of CAP patients with determined pathogens ($p = .376$). In both groups, *M. pneumoniae*

was reported even less frequently (0.9% in NHAP vs 4.8% in CAP; $p = .052$), and the occurrence of *C. pneumoniae* was not reported. From January 2012 through April 2013, Korean investigators, Koh et al,³² also examined the microbial etiology of elderly patients hospitalized with CAP or NHAP. In contrast to the previously mentioned studies, Koh et al utilized a retrospective study design and relied on medical records for their investigation. Again, there was a low occurrence of atypical bacteria. However, the frequency of *M. pneumoniae* in NHAP was not statistically different than that in CAP (6 patients in NHAP, 5 patients in CAP; $p = .076$). *L. pneumophila* occurred in none of the NHAP cases, and the incidence of *C. pneumoniae* was not reported.³²

Three prospective cohort studies enrolling ICU patients in this review found a small role of atypical bacteria in NHAP.^{10,11,33} In 2010, Polverino et al³³ published a 10-year study of all consecutive cases of NHAP admitted to a hospital in Barcelona, Spain, from 1997 to 2007. Of the 150 cases enrolled, 20 patients required intensive care. Microbial etiology was established in 38% (57/150) of NHAP admissions, and atypical bacteria were found infrequently among these patients. *Legionella pneumophila* was the most common, occurring in 5% of NHAP patients with confirmed microbial etiologies. Two cohort studies by El-Solh and colleagues conducted from 1996 to 1999 and then from 1999 to 2001 enrolled only patients admitted to the ICU.^{10,11} In this first prospective cohort study, patients 75 years of age and older and admitted to the ICU with the diagnosis of pneumonia requiring mechanical ventilation were included.¹⁰ Of the 104 patients enrolled, 47 were admitted from nursing homes and 57 were admitted from home (eg, CAP). Microbial etiology was determined in 53% of all participants. In the nursing home cohort, atypical bacteria were not identified, although *C. pneumoniae* and *Legionella* were identified in 2% and 9% of CAP patients. In the second cohort by El-Solh et al,¹¹ participants were required to have failed 72 hours of antimicrobial treatment in the nursing home prior to enrollment and were admitted to the ICU. Once again, El-Solh et al demonstrated a low incidence of atypical pathogens among the study's 52 critically ill nursing home residents.

Two studies in this review explored the clinical and microbial characteristics of NHAP as either a subset of the broader HCAP category, as defined by IDSA guidelines in 2005, or as a component of an entirely new pneumonia class. In a retrospective,

comparative review of 202 patients admitted to a Japanese hospital with pneumonia, Umeki and colleagues³⁴ divided patients into 3 categories: CAP, NHAP, and the “other than NHAP” group referred to as O-HCAP. The O-HCAP group was comprised of patients meeting the IDSA’s definition of HCAP (ie, recent hospitalization, dialysis, wound care, or intravenous antibiotics or chemotherapy) with the exception of nursing home residence. Atypical bacteria were most common in the CAP group, occurring in 5.7% of patients, followed by 4.3% of patients in the NHAP, and not at all in the O-HCAP group (CAP vs NHAP; $p = 1.000$).³⁴ After Japan’s 2011 introduction of a new pneumonia category, NHCAP or nursing and healthcare-associated pneumonia, Japanese investigators Miyashita and colleagues³⁵ examined the microbial etiology of NHCAP cases presenting to a university hospital (250 patients) and a community hospital (349 patients). The NHCAP category in this study was composed of 4 different subsets as defined by the Japanese Respiratory Society guidelines: (1) nursing home residence, (2) hospitalization within the last 90 days, (3) elderly or physically disabled patients requiring health care, and (4) ambulatory patients receiving endovascular therapy (dialysis, intravenous antibiotics, chemotherapy, or immunosuppressants). Atypical bacteria were found to be more common in CAP cases admitted to the university hospital (16% of patients) or community hospital (14% of patients) compared to NHCAP cases (0.8% and 1% of patients admitted to the university and community hospitals, respectively; CAP vs NHCAP; $p < .0001$). However, the role of atypical bacteria in the first category (NHAP) of the NHCAP definition was not specifically reported.³⁵

DISCUSSION

In 3 of the 13 studies reviewed, atypical bacteria, specifically *C. pneumoniae*, were found to be frequent etiologic pathogens of NHAP in hospitalized patients^{20–23} with rates similar to that of matched CAP cohorts.^{22,23} In the majority of studies, atypical bacteria were detected infrequently in NHAP^{10,11,26–35}; although in multiple studies, rates were not statistically different than that in non-ICU CAP cohorts.^{29,32,34} The low yield of atypical bacteria in several studies may be partially explained by suboptimal microbial investigations. Atypical bacteria are so-called “atypical” because of the inability to culture *Chlamydia*, *Mycoplasma*, and *Legionella* on standard media, making the identification of these pathogens

a significant diagnostic challenge.⁹ With the exception of *Legionella pneumophila* serogroup 1, which can be detected via urinary antigen, the diagnosis of *Chlamydia* and *Mycoplasma* has traditionally relied on serologic testing with the collection of appropriately paired acute and convalescent sera. Such serology samples are not routinely obtained in clinical practice and may be inconsistently collected—and sometimes not collected at all—in etiologic studies of NHAP.⁹ This is true of the previously published review of 18 studies on the microbial etiology of NHAP from 1978 to 1994 by Muder et al in which *C. pneumoniae* and *M. pneumoniae* bacteria were identified in only 2 studies, with a reported incidence of 1% and 6%, respectively.¹⁹ Yet very few studies in the Muder et al review were specifically designed to identify atypical bacteria.¹⁹

In the current review, the frequency of atypical bacteria in enrolled cohorts was reported in all studies, although microbial investigations were often not detailed^{26,29,32,33} or did not strictly adhere to accepted standards for diagnosing atypical bacteria, specifically *C. pneumoniae*,^{10,11,23,24,27,34} as outlined in Table 2. In an effort to standardize approaches for diagnosing *C. pneumoniae*, the Centers for Disease Control and Prevention (CDC) published recommendations in 2001.³⁶ For serology testing, the CDC defined an acute infection of *C. pneumoniae* as a 4-fold increase in paired serum IgG titers or a single IgM titer greater than or equal to 1:16.³⁶ In addition, the collection of serum samples must be appropriately timed to account for a delayed antibody response. The IgM antibody to *C. pneumoniae* is detectable 2 to 3 weeks after illness onset, whereas detection of the IgG antibody may take 6 to 8 weeks to achieve high enough titers. The use of a single IgG titer for determining acute infection is also discouraged by the CDC, because in cases of reinfection, IgG may be elevated but IgM may not be detected.³⁶ For *M. pneumoniae*, the CDC does not currently provide recommendations for standardizing its diagnosis, although similar concepts would apply: IgG titers should be paired to detect a 4-fold rise or a single IgM titer performed at least 1 week after illness onset.^{37,38}

In this review, paired sera for *C. pneumoniae* detection were often collected infrequently^{11,26} or were not well described.^{29,32} For instance, in the study by Ma et al in 2012, serology samples were collected in just 14% (69/488) of patients; accordingly, the presence of atypical bacteria was detected in only 2 patients.²⁶ In the 2001 El-Solh et al study

Table 2. Microbial investigations for *Chlamydia pneumoniae*

Study [ref]	Year ^a	Serology sampling				NPA PCR	Meets CDC serology recommendation ^c
		Definition of positive IgG	Serology IgM performed	Timing of paired serum sample ^b	Serology test		
Koh et al [32]	2015	4-fold increase in paired sera or titer >64	NR	NR	NR	Not enough information	Koh et al [32]
Ma et al [27-28]	2013	4-fold increase in paired sera	Yes	2 weeks	CF	Yes	No
Ewig et al [29-31]	2012	NR	NR	NR	NR	NR	Not enough information
Ma et al [26]	2012	4-fold increase in paired sera	Yes	NR	NR	No	Not enough information
Miyashita et al [35]	2012	4-fold increase in paired sera	Yes	≥ 4 weeks	MIF	Yes	Yes
Umeki et al [34]	2011	Based on index values ^e	Yes	NR	EIA	No	No
Maruyama et al [22]	2010	4-fold increase in paired sera	Yes	2-8 weeks ^d	MIF	No	Yes
Polverino et al [33]	2010	4-fold increase in paired sera	No	4-6 weeks	NR	NR	Not enough information
Lui et al [25]	2009	4-fold increase in paired sera	Yes	>2 weeks	EIA, CF	No	No
Maruyama et al [20-21]	2008	4-fold increase in paired sera	Yes	2-8 weeks	MIF	No	Yes
El-Solh et al [11]	2002	4-fold increase in paired sera	No	>4 weeks	MIF ^d	NR	No
El-Solh et al [10]	2001	4-fold increase in paired sera	No	4-6 weeks	MIF	No	No
Lim et al [23-24]	2001	3-fold increase (EIA); 4-fold in paired sera (CF)	Yes	4-6 weeks after discharge	EIA, CF	No	No

Note: CF = complement fixation; EIA = enzyme immunoassay; MIF = microimmunofluorescence; PCR = polymerase chain reaction; NPA = nasopharyngeal aspirate; NR = not reported.

^a Year published.

^b Timing of convalescent serum sample in relation to acute phase serum collection.

^c CDC recommendation: MIF test to detect 4-fold increase in IgG *C. pneumoniae* antibodies or an IgM titer ≥1:16. Convalescent serum should be obtained 6-8 weeks after infection to detect both IgM and IgG antibodies (2-3 weeks for IgM alone). Use of single IgG titers is discouraged.

^d Assumed to be similar to the previous study by same authors, although not reported in newer study.

^e Concentrations of IgG antibodies against *C. pneumoniae* expressed as the IgG index. Positive IgG defined as an index value ≥ 1.10 or increase of 1.35 in index for paired sera.

of 136 patients, only 57 serology samples were collected, with a greater proportion of serological investigations performed on community-dwelling patients than nursing home patients ($p < .02$).¹⁰ Moreover, the CDC recommends waiting 6 to 8 weeks for collection of convalescent sera, but none of the studies in this review strictly followed this recommendation, with some studies allowing collection of convalescent

sera as early as 2 weeks^{20-23,27} or 4 weeks^{10,11,24,33,35} after the first sample. For the studies in which single *C. pneumoniae* IgM titers were drawn, the timing of collection was either not specified^{22,26,34,35} or occurred within 24 to 48 hours of hospital admission.^{20,23,25,27} As previously discussed, 2 to 3 weeks after illness onset is often needed to detect appreciable levels of *C. pneumoniae* IgM antibodies.³⁶

Although several serological methods exist for *C. pneumoniae*, the CDC only endorses the use of the microimmunofluorescence (MIF) test.³⁶ Other serology methods include complement fixation (CF) tests and enzyme immunoassay (EIA). The Maruyama et al, El-Solh et al, and Miyashita et al studies utilized the MIF test in accordance with CDC recommendations for *C. pneumoniae* diagnosis, whereas 4 studies used either CF or EIA tests.^{23-25,27,34} Many studies did not report the test used.^{26,29,32,33} The only studies that used the MIF test and mostly adhered to the CDC recommendations for collection of paired sera for detection of *C. pneumoniae* were the 2008 and 2010 studies published by Maruyama and colleagues and the 2012 NHAP study by Miyashita et al.^{20,22,35} Despite adherence to *C. pneumoniae* diagnostic criteria, the results of the Maruyama et al studies and the Miyashita et al study disagree on the role of atypical bacteria. Both Maruyama et al studies report a high incidence of *C. pneumoniae* with this pathogen present in nearly 50% of NHAP patients with confirmed microbial etiologies.^{20,22} Conversely, the Miyashita et al study reports a negligible role of atypical bacteria in the NHAP group despite the use of culture and polymerase chain reaction (PCR) testing in addition to serology testing.³⁵ Yet the heterogeneity of the NHAP group with nearly two-thirds of patients with HCAP risk factors other than NHAP may partially explain the lower incidence of atypical bacteria in the Miyashita et al study. In the Maruyama et al studies, a high incidence of atypical bacteria was found among all patients: 35% (13/37) of CAP patients with confirmed microbial etiologies were found to have acute infection with *C. pneumoniae* in the 2010 study as were 35% (9/26) of HAP patients with determined etiologies in the 2008 study.^{20,22} Outbreaks of respiratory illness due to atypical bacteria, specifically *C. pneumoniae*, have been reported in nursing homes worldwide and are often characterized by high attack rates due to its airborne transmission.³⁹⁻⁴⁹ Thus, the high rate of *C. pneumoniae* among all patients in the 2008 and 2010 Maruyama et al studies could be the result of a *C. pneumoniae* outbreak. Yet in their 2010 study, Maruyama and colleagues reported an even distribution of atypical bacteria at Kinan General Hospital during the June 2004 and May 2005 study period. This was also the location and time frame for the earlier 2008 study.²² Such an even distribution of atypical bacteria throughout the year would make it less likely that an outbreak was responsible for the high frequency of *C. pneumoniae* in the Maruyama et al studies.

Several limitations exist in this review, including a lack of adherence to CDC recommendations for *C. pneumoniae* identification as well as the lack of conformity in diagnostic strategies across the studies. Moreover, the studies with the greatest adherence to serological recommendations in this review were conducted in Japan, which may limit the generalizability of the findings of studies such as Maruyama et al to other countries. With its “unique nursing care insurance system” for patients 65 years of age and older, the definition of a Japanese nursing home may very well differ from that used in the United States or other countries.¹⁷ There is also limited information from these studies on whether empiric atypical coverage actually leads to improved clinical outcomes in NHAP. In the study by Lim et al, about half of the CAP patients and NHAP patients with identified atypical bacteria did not receive atypical antibiotic coverage, but all 6 of these patients still survived.²³ Similarly, no deaths were reported in 10 of 11 patients with atypical infection not receiving atypical antibiotic coverage in the 2013 Ma et al study of NHAP patients.²⁷ Similar mortality findings were found in a 2014 non-inferiority trial conducted by Garin et al.⁵⁰ In this open-label, multicenter, randomized trial of 580 hospitalized patients with moderately severe CAP, the role of combination beta-lactam and macrolide therapy was compared to beta-lactam therapy alone.⁵⁰ Mortality, length of hospital stay, and ICU admission were similar between study groups; however, 30-day readmissions and clinical instability after 7 days of treatment were more likely in the beta-lactam alone arm than in the combination treatment group. In addition, patients specifically with atypical bacteria were significantly less likely to achieve clinical stability with beta-lactam monotherapy (hazard ratio [HR], 0.33; 95% CI, 0.13-0.85). Although patients residing in a nursing home were excluded from this study, 25% of study participants were over the age of 84 years with evidence of chronic disease.⁵⁰ In a published prediction model, nursing home residence was found highly predictive of *C. pneumoniae* pneumonia in hospitalized patients (odds ratio [OR], 3.73; 95% CI, 1.39-10.06); thus, extrapolating the findings of Garin et al to hospitalized patients with NHAP may be not only appropriate but also imperative.⁵¹

Future Directions

In order to accurately define the role of atypical bacteria in NHAP, more studies specifically designed to identify atypical bacteria using validated diagnostic methods are needed. To accomplish this, advances

in diagnostic technology may also be necessary. Fortunately, promising technology may be on the horizon with the first commercial PCR assay approved by the US Food and Drug Administration in 2012 for the simultaneous detection of *C. pneumoniae* and *M. pneumoniae* using a single nasopharyngeal swab.⁵² In the United States, in particular, trials evaluating the etiology of NHAP outside of the ICU are needed, as the US studies by El-Sohl et al were conducted solely in critically ill patients. In addition, the microbial landscape of NHAP may differ from country to country, thus country-specific endeavors may be needed to determine appropriate management of NHAP in the United States and elsewhere. Lastly, mixed pathogens were reported in patients with NHAP in several studies in this review; therefore, more evidence is needed to examine the role of atypical bacteria as a single causative agent in NHAP and as a potential co-pathogen.^{10,20-22,25}

Conclusion and Implications for Practice

With the lack of rigorous investigations for atypical bacteria in this review, a large body of evidence is unavailable to accurately describe the role of atypical bacteria in NHAP. The 2008 and 2010 Maruyama et al studies may provide the most convincing information about atypical bacteria in NHAP, with their greatest adherence to available microbial diagnostic criteria. However, with a high rate of *C. pneumoniae* infection in all patients within the Maruyama et al studies, even those with late-onset HAP, the results of both the 2008 and 2010 studies may be questioned. Nevertheless, in the majority of studies comparing NHAP to CAP in this review, the frequency of atypical bacteria was similar although often infrequent. Suboptimal microbial investigations may account for this low prevalence of atypical bacteria, but more studies will be needed to disprove this assumption.

Based on the results of this review, implications for practice are limited with the exception of one distinction: serologic testing does not offer early detection of *C. pneumoniae* or *M. pneumoniae* and is, at best, a tool for epidemiologic studies when properly performed.^{36,37} New PCR technology is being developed, but the cost of equipment and supplies may limit routine use for some time. Without access to reliable assays for diagnosis of atypical bacteria or rigorous microbial studies, the role of atypical bacteria in NHAP is unclear and the debate on whether hospitalized nursing home residents should be treated in accordance with CAP or nosocomial pneumonia guidelines continues.^{7-9,18} To bridge the

guideline gap, clinicians treating NHAP may look to a recently published set of practical recommendations from the University of Virginia.¹³ In this 2015 publication, NHAP is categorized as either uncomplicated or complicated, with authors suggesting that uncomplicated NHAP be treated as a form of CAP with coverage for atypical bacteria. A broader HCAP or HAP antibiotic regimen may, however, be appropriate for patients with complicated NHAP as evidenced by severe illness—mechanical ventilation, ICU admission, lack of improvement after 72 hours—or the presence of chronic wounds, antibiotic use in the past 90 days, recent hospitalization, colonization with MDR organisms, or residence in a facility with a high prevalence of MDR organisms.¹³ Japan's NHCAP guideline recommends a similar strategy for nursing home residents hospitalized with pneumonia: Antipseudomonal or MRSA coverage should be considered only upon admission to the ICU or in the presence of additional risk factors for MDR organisms such as a recent antibiotic therapy, hospitalization within the past 3 months, or MRSA colonization.¹⁷ In these patients, atypical coverage can also be considered, especially in known outbreaks or in severe cases requiring ICU care due to the severity of illness caused by *Legionella*. In the absence of these risk factors, Japan's NHCAP guideline states that the common respiratory pathogens—*Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, and *Chlamydia pneumoniae*—or anaerobes, in the case of aspiration pneumonia, should be targets of empiric antimicrobial therapy in NHAP. The authors of the 2016 HAP guideline “anticipate” a similar strategy for patients previously classified under the HCAP definition.¹⁸ The addition of antibiotic therapy for MDR organisms would “likely be based on validated risk factors for MDR pathogens” and “not solely on whether or not the patient had previous contacts with the healthcare system.”¹⁸ Until future studies and guidelines can fully elucidate the role of atypical bacteria in NHAP, these approaches may serve as practical solutions to an unanswered question.

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