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The Effect of Macrolides on Mortality in Bacteremic Pneumococcal Pneumonia: A Retrospective, Nationwide Cohort Study, Israel, 2009–2017

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Background. Previous cohort studies of pneumonia patients reported lower mortality with advanced macrolides. Our aim was to characterize antibiotic treatment patterns and assess the role of quinolones or macrolides in empirical therapy.

Materials. An historical cohort, 1 July 2009 to 30 June 2017, included, through active surveillance, all culture-confirmed bacteremic pneumococcal pneumonia (BPP) among adults in Israel. Cases without information on antibiotic treatment were excluded. Logistic regression analysis was used to assess independent predictors of in-hospital mortality.

Results. A total of 2016 patients with BPP were identified. The median age was 67.2 years (interquartile range [IQR] 53.2–80.6); 55.1% were men. Lobar pneumonia was present in 1440 (71.4%), multi-lobar in 576 (28.6%). Median length of stay was 6 days (IQR 4–11). A total of 1921 cases (95.3%) received empiric antibiotics with anti-pneumococcal coverage: ceftriaxone, in 1267 (62.8%). Coverage for atypical bacteria was given to 1159 (57.5%), 64% of these, with macrolides. A total of 372 (18.5%) required mechanical ventilation, and 397 (19.7%) died. Independent predictors of mortality were age (odds ratio [OR] 1.051, 95% confidence interval [CI] 1.039, 1.063), being at high-risk for pneumococcal disease (OR 2.040, 95% CI 1.351, 3.083), multi-lobar pneumonia (OR 2.356, 95% CI 1.741, 3.189). Female sex and macrolide therapy were predictors of survival: (OR 0.702, 95% CI .516, .955; and OR 0.554, 95% CI .394, .779, respectively). Either azithromycin or roxithromycin treatment for as short as two days was predictor of survival. Quinolone therapy had no effect.

Conclusions. Empirical therapy with macrolides reduced odds for mortality by 45%. This effect was evident with azithromycin and with roxithromycin. The effect did not require a full course of therapy.

Keywords. pneumococcal pneumonia; azithromycin; roxithromycin; mortality.

Community-acquired pneumonia is a common cause of hospitalization and death. Empirical therapy guidelines for the treatment of community-acquired pneumonia in hospitalized patients recommend either combination therapy with a β-lactam and an advanced macrolide (azithromycin or clarithromycin) or mono-therapy with respiratory quinolones [1]. Randomized controlled trials (RCT) showed equivalence of both options. Most RCT that assessed therapies for pneumonia were small or did not enroll sizable numbers of patients with severe disease [2–5]. Moreover, the majority were non-inferiority studies. Yet several large observational studies of hospitalized patients with severe disease found decreased mortality in patients receiving β-lactam and a macrolide versus either β-lactam alone or respiratory quinolones [6–11]. This effect was described in patients with a defined final diagnosis of bacteremic pneumococcal pneumonia (BPP), even in the setting of macrolide resistance [6, 11, 12]. This suggests an anti-inflammatory effect of the macrolides, such as inhibition of pneumolysin, rather than their antibacterial properties, an effect not shared with quinolones [13–15].

In Israel, roxithromycin is one of the macrolides used for combination therapy in pneumonia, but no information was available about the possible effect of this macrolide on mortality. Another unanswered question in the literature was the duration of macrolide therapy required to ensure a possible beneficiary effect, once a specific diagnosis is available.

The objective of this study was to characterize antibiotic therapy patterns in a cohort of patients with BPP and to study the effect of macrolide treatment on mortality.

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METHODS

This study was a part of an ongoing, nationwide, prospective, population-based, active surveillance of pneumococcal bacteremia adult cases, initiated on 1 July 2009. Data collected until 31 June 2017 were included. The surveillance included all 26 hospitals and 1 major outpatient health maintenance organization (Maccabi Healthcare Services central laboratory) in Israel that routinely obtain blood and cerebrospinal fluid (CSF) cultures. Fewer than 1% of blood cultures and no CSF cultures are obtained outside these centers. This enabled us to cover almost all culture-confirmed BPP cases in the Israeli adult population [16].

Case Definition

A BPP case was defined by isolation of *Streptococcus pneumoniae* from blood, with infiltrates on imaging. Diagnoses based solely on non-culture methods (polymerase chain reaction, antigen testing, gram stain or clinical diagnosis only) were excluded. To assure >95% reporting, several collection methods were conducted. All invasive *S. pneumoniae* isolates are legally required to be reported and sent to the Ministry of Health (MOH) reference laboratory. In addition to this passive surveillance, active surveillance using a capture-recapture method took place as described previously. Cases with no information on antibiotic treatment were excluded.

Risk Group Definition

Patients at-risk were defined as those with alcoholism, chronic heart disease, liver disease, or lung disease (including chronic obstructive pulmonary disease, emphysema, asthma) and diabetes mellitus. High-risk patients were defined as those with sickle cell disease or other hemoglobinopathies, anatomic or functional asplenia, congenital or acquired immunodeficiency, human immunodeficiency virus (HIV) infection, chronic renal failure or nephrotic syndrome, leukemia, lymphoma, Hodgkin disease, solid organ transplant, multiple myeloma, generalized and metastatic malignancies, or therapy-induced immunosuppression, including radiation therapy [17].

Data from the electronic medical records of all cases were collected retrospectively within 2–3 months of hospitalization by investigators of the Israeli Adult Invasive Pneumococcal Disease (IAIPD) group. Data collected included sociodemographics (sex, age), medical history including any comorbidity, IPD-predisposing comorbidities (diabetes mellitus, chronic renal failure, congestive heart failure, lung disease, HIV, immunodeficiency, spleen deficiency, malignancy, and prior neurosurgery), substance abuse, or smoking history. Antibiotic treatment during hospitalization was collected; empirical therapy was the first treatment initiated from a day before to a day after blood cultures were taken. A switch/change was the first change in antibiotics while in hospital. In-hospital complications and outcome (intensive care unit [ICU] admission, mechanical ventilation, and in-hospital mortality) were also collected.

All centers assessed susceptibility to penicillin, ceftriaxone and erythromycin following Clinical and Laboratory Standards Institute guidelines (http://www.clsi.org/source/custom/currentdocs.cfm).

Statistical Analysis

Descriptive analysis of treatment patterns was performed using R statistical software, version 3.6.0. Treatment patterns include single treatment, prolongations and switches. Treatment switches were defined as consecutive antibiotic treatment episodes. In switch classification, a delay of 24 hours between treatment episodes was acceptable. Overlapping treatments of at least 3 days or prolongation of the same antibiotic class were considered the same treatment episode. Transition between overlapping or combination treatments in the same patient were counted as separate events.

For predictors of mortality, continuous variables were assessed using t test or Mann-Whitney, as appropriate. The χ^2test was used for dichotomous variables. Logistic regression for mortality as a dependent variable was performed using significant variables with $P < .05$. Data were analyzed using SPSS, version 27 (IBM Corp., Armonk, New York, USA).

Ethics committee approval: Sheba 7415-09.

RESULTS

Over the 8 years of the study, 2161 patients with BPP were identified. Of those, 145 (6.7%) did not have any information on antibiotic treatment and were excluded. The study included 2016 BPP patients. The median age was 67.2 years (interquartile range [IQR] 53.2–80.6), and 55.1% were men. A total of 627 (31.1%) had no risk-factors for IPD, 588 (29.2%) were at risk, and 801 (39.7%) were high risk for IPD. Most infections were acquired in the community and only 68 (3.4%) were nosocomial. Median length of stay (LOS) was 6 days (IQR 4–11) and 15.3% were admitted to the ICU, 18.5% required mechanical ventilation and 397 (19.7%) died. High level penicillin resistance was uncommon, occurring in only 44 (2.3%) of the cases and high-level ceftriaxone resistance was rare (3 cases, 0.2%). Clinical severity index at admission was not available, but involvement of a single lobe (1440, 71%),versus multi-lobar (576, 29%) provided a proxy for severity. Mortality was 15.7% in lobar versus 29.7% in multi-lobar pneumonia (Table 1).

A total of 95.3% (1921 cases) of the cohort received empiric antibiotics with anti-pneumococcal coverage. The commonly given drug was ceftriaxone, in 1267 cases (62.8%). Second generation cephalosporin was given to 246 cases (12.2%), and penicillin, piperacillin-tazobactam, and respiratory quinolones

Table 1. Demographics and Empiric Therapy According to Clinical Severity (A Patient Could Receive More Than One Treatment)

Variable	Single Lobe	Multi-Lobar	*P*-value	Total Pneumonia (2016)
Age, median (IQR)	66.5 (53.3–79.9)	68.9 (52.3–82.6)	<.001	67.2 (53.2–80.6)
Sex, male	792 (55.1%)	318 (55.2%)	.96	1110 (55.1)
Risk category			.10	
No risk	460 (31.9%)	167 (29%)		627 (31.1%)
At risk	429 (29.8%)	159 (27.6%)		588 (29.2%)
High risk	551 (38.3%)	250 (43.4%)		801 (39.7%)
Mortality	226 (15.7%)	171 (29.7%)	<.001	397 (19.7%)
Anti-pneumococcal therapy	1376 (95.6%)	545 (94.6%)	.37	1921 (95.3%)
Ceftriaxone	916 (63.6%)	351 (60.9%)	.26	1267 (62.8%)
Second generation cephalosporin	198 (13.8%)	48 (8.3%)	<.001	246 (12.2%)
Pipril-Tazobactam	128 (8.9%)	86 (14.9%)	<.001	214 (10.6%)
Respiratory quinolones	152 (10.6%)	58 (10.1%)	.75	210 (10.4%)
Vancomycin	68 (4.7%)	38 (6.6%)	.09	106 (5.3%)
Penicillin	66 (4.6%)	26 (4.5%)	.95	92 (4.6%)
Augmentin	72 (5%)	19 (3.3%)	.1	91 (4.5%)
Other	108 (7.5%)	70 (12.2%)	<.001	178 (8.8%)
Atypical	848 (58.7%)	311 (54.0%)	.043	1159 (57.5%)
Macrolide	549 (38.1%)	197 (34.2%)	.1	746 (37%)
Azithromycin	374 (26%)	161 (28%)	.36	535 (26.5%)
Roxithromycin	175 (12.2%)	36 (6.3%)	<.001	211 (10.5%)
Respiratory quinolone	152 (10.6%)	58 (10.1%)	.75	210 (10.4%)
Quinolone	126 (8.8%)	53 (9.2%)	.75	179 (8.9%)

Abbreviation: IQR, interquartile range.

were each given to about 10% of the cohort, respectively (Table 1). Atypical coverage of either combination therapy with macrolides, quinolones, or respiratory quinolones as single therapy was given to 1159 (57.5%) of cases. Macrolides were used in 746 cases (64.4%) of atypical coverage.

In a total of 1246 individuals, no change in antibiotic therapy was done up to their discharge, even though microbiology results were available. Macrolides were given up until discharge in 481/2016 (23.9%) of the cohort.

In 770 (38.2%) individuals, one or more antibiotics were changed (either replaced or stopped) during hospitalization. The median time to change was 3.5 days (IQR 2.5-5.5). The most common change during hospitalization was discontinuation of atypical therapy (292 cases, 14.5% of the cohort), which included cessation of macrolides in 266 cases.

Mortality

We assessed predictors of mortality, influenced by treatment. Thus, outcome was mortality from 72 hours after admission to discharge, thus for this assessment excluded were 171 patients (8.5%) who died in the first 72 hours. In a univariate analysis, advanced age, male sex, higher risk status, and lobar versus multi-lobar pneumonia were all related to increased mortality (Table 2). Empirical therapy with atypical pathogens treatment decreased mortality significantly. A total of 62.0% (1004/1619) of the patients surviving BPP received atypical pathogen therapy (a macrolide or a quinolone), compared to only 42.9% (97/226) of non-survivors. This effect was similar for both single and multi-lobar pneumonia. Quinolones as part of atypical empirical therapy did not influence mortality: 19.5% of survivors received quinolones versus. 21.2% of non- survivors ($P = .53$). However, macrolide therapy had a significant effect (40.9% of survivors vs. 23% of non-survivors, $P < .001$). The effect was evident for azithromycin (29% of survivors received azithromycin vs. 17.7% of non-survivors, $P < .001$), as well as for roxithromycin (11.9% of survivors received roxithromycin compared to 5.3% of non-survivors, $P = .003$). However, few patients with multi-lobar pneumonia received roxithromycin; thus, the difference did not reach statistical significance ($P = .19$). In a multivariate logistic model, independent predictors of mortality were age (odds ratio [OR] 1.051, 95% confidence interval [CI] 1.040, 1.063) high-risk group for pneumococcal infection (OR 2.040, 95% CI 1.351, 3.083), and having multi-lobar pneumonia (OR 2.356, 95% CI 1.741, 3.189) (Table 3). Female sex (OR 0.702, 95% CI .516, .955) and empiric use of macrolides (OR 0.554, 95% CI .394, .779) were predictors of survival. Two sensitivity analysis of mortality predictors were preformed; one including vancomycin treatment, as it was related to worse outcome (Supplementary Table 1), and the second sensitivity analysis was done for all in-hospital death, including deaths in the first 72 hours after admission (Supplementary Table 2). The effect of macrolides remained.

Because therapy with atypical coverage is often discontinued once the diagnosis of BPP is evident, we wanted to assess whether treatment with two days of macrolides was sufficient for the protective effect on mortality. To overcome immortality

Table 2. Mortality From 72 hours After Admission to Discharge

	Lobar			Multi-lobar			Total		
Variable	Alive 1214	Dead 126	*P*-value	Alive 405	Dead 100	*P*-value	Alive 1619	Dead 226	*P*-value
Age, years (SD)	626 (18.7)	77 (14.6)	<.001	61.6 (20)	75.9 (14.4)	<.001	62.3 (19.4)	76.6 (14.4)	<.001
Sex, male	667 (55%)	76 (60.3%)	.26	212 (52.3%)	66 (66%)	.002	879 (54.4%)	142 (62.8%)	.02
Risk status			<.001			.02			<.001
No risk	428 (35.3%)	17 (13.5%)		129 (31.9%)	19 (19%)		557 (34.4%)	36 (15.9%)	
At risk	357 (29.4%)	39 (30%)		114 (28.1%)	27 (27%)		471 (29.1%)	66 (29.2%)	
High risk	429 (35.3%)	70 (55.6%)		162 (40%)	54 (54%)		591 (36.5%)	124 (54.9%)	
Empiric anti-pneumococcal	1169 (96.3%)	114 (90.5%)	.002	384 (94.8%)	96 (96%)	.78	1553 (95.8%)	210 (93.0%)	.06
Atypical	759 (62.5%)	56 (44.4%)	<.001	245 (60.5%)	41 (41%)	.001	1004 (62%)	97 (42.9%)	<.001
Total duration, days (SD)	5 (3.5)	6.2 (4.8)	.049	5.7 (5.7)	7.1 (6.9)	.134	5.2 (4.1)	6.6 (5.8)	.01
Quinolone	239 (19.7%)	26 (20.6%)	.8	78 (18.8%)	22 (22.0%)	.48	315 (19.5%)	48 (21.2%)	.53
Empiric macrolide	496 (40.9%)	32 (24.4%)	<.001	166 (41%)	20 (20%)	<.001	662 (40.8%)	52 (22.7%)	<.001
Duration of macrolide			.002			.002			<.001
None	731 (60.2%)	95 (75.4%)		247 (61%)	80 (76%)		978 (60.4%)	175 (77.4%)	
Short ≤2 days	191 (15.7%)	9 (7.1%)		92 (22.7%)	13 (13%)		257 (17%)	16 (7.1%)	
Long ≥3 days	292 (24.1%)	22 (17.5%)		92 (22.7%)	13 (13%)		384 (24.7%)	35 (15.5%)	
Azithromycin	333 (27.4%)	24 (19%)	.04	139 (33.6%)	16 (16%)	.001	475 (29%)	40 (17.5%)	<.001
Roxithromycin	163 (13.4%)	8 (6.3%)	.02	29 (7.0%)	4 (4.0%)	.27	192 (11.9%)	12 (5.3%)	.003
Antibiotic switch	484 (39.9%)	47 (37.3%)	.63	174 (43%)	45 (45%)	.74	658 (40.6%)	92 (40.7%)	.98
Penicillin			.32			.52			.15
sensitive	922 (78.3%)	88 (73.3%)		308 (76.2%)	68 (70.8%)		1225 (77.9%)	156 (72.2%)	
Intermediate	235 (19.9%)	28 (23.3%)		80 (20.3%)	25 (26%)		315 (20.0%)	53 (24.5%)	
resistant	21 (1.8%)	4 (3.3%)		12 (3%)	3 (3.1%)		33 (2.1%)	7 (3.2%)	
Ceftriaxone			.87			.40			.28
sensitive	1115 (94.7%)	111 (94.1%)		364 (92.4%)	84 (89.4%)		1479 (94.1%)	195 (92.0%)	
Intermediate	60 (5.1%)	7 (5.9%)		31 (7.4%)	10 (10.6%)		90 (5.7%)	17 (8.0%)	
resistant	3 (0.3%)	0					3 (0.2%)	0	
Macrolide			.01			.78			.1
sensitive	921 (89.8%)	78 (78.8%)		306 (86.2%)	76 (89.4%)		1227 (88.9%)	154 (83.7%)	
Intermediate	2 (0.2%)	0		3 (0.8%)	1 (1.2%)		5 (0.4%)	1 (0.5%)	
resistant	103 (10)	21 (21.2%)		45 (12.7%)	8 (9.4%)		148 (10.7%)	29 (15.8%)	

Abbreviation: SD, standard deviation.

Table 3. Independent Predictors for In-Hospital Mortality: Macrolide as Empirical Therapy Versus No Macrolide Therapy

Variable	Odds Ratio	95% CI	*P*-value
Age	1.051	1.040, 1.063	<.001
Sex (female)	0.702	.516, .955	.024
Risk category			<.001
No risk	1		
At risk	1.216	.775, 1.910	.394
High risk	2.040	1.351, 3.083	<.001
Multi lobar vs. lobar	2.356	1.741, 3.189	<.001
Macrolide therapy	0.554	.394, .779	<.001

Abbreviation: CI, confidence interval.

bias, that is, patients who received treatment for longer duration, had to survive longer, we assessed the effects of no treatment with macrolide, treatment with macrolide of up to two days or longer treatment on mortality from 72 hours after admission to discharge. As can be seen in Table 4, the association with survival remained significant for short therapy (≤2 days) versus none with an OR of 0.440 (95% CI .254, .764).

DISCUSSION

Based on Israeli nationwide data of all IPD cases in the years 2009–2017, we identified 2016 patients with BPP and data on in-hospital antibiotic treatment. Independent predictors of death were advanced age, male sex, multi-lobar pneumonia, and having comorbidities related to high-risk for pneumococcal disease. Empirical treatment with a macrolide, either azithromycin or roxithromycin, in combination with beta-lactam therapy was predictive of survival, and decreased odds for mortality by 45%. Macrolide treatment as short as 2-day duration was sufficient to afford this effect, which was not seen with quinolones.

Similar effects were seen in several observational cohort studies. The cohort study by Martinez et al. included 409 patients with BPP, of whom 238 received beta-lactam plus macrolide. Empirical macrolide therapy was associated with

Table 4. Independent Predictors for In-Hospital Mortality: Effect of Macrolide Therapy Duration

Variable	Odds Ratio	95% CI	*P*-value
Age	1.051	1.040, 1.063	<.001
Sex (female)	0.705	.518, .959	.026
Risk category			
No risk	1		.008
At risk	1.217	.775, 1.910	.393
High risk	2.062	1.365, 3.115	<.001
Pneumonia severity	2.359	1.743, 3.194	<.001
Macrolide therapy			.004
Short therapy ≤2 days	0.440	.254, .764	.004
Long therapy ≥3 days	0.661	.443, .988	.043

Abbreviation: CI, confidence interval.

protective effect against mortality, with an OR of 0.4 (95% CI .17, .92) [12]. No comparison to quinolones was done, and the group that received macrolide were less likely to include HIV patients and patients with hematological malignancies. In a single center study of 1715 patients with known etiology of pneumonia, patients receiving beta-lactam plus macrolide had lower mortality compared to patients receiving quinolones. This effect was evident only in cases of pneumococcal pneumonia with high inflammatory response [7]. In another cohort study that assessed 140 ICU patients with pneumococcal pneumonia, treatment with azithromycin resulted in fewer deaths compared to non-macrolide therapy (OR 0.27), regardless of macrolide resistance [11]. Studies assessing patients with severe pneumonia, found similar effects in patients with bacteremic pneumonia caused by other pathogens, with pneumonia severity index ≥5, or hospitalized in the ICU [8–10]. Thus, it seems that the effect is related to the severity of the pneumonia, rather than specifically to pneumococcal pneumonia. Our study, which includes the largest cohort of BPP so far, adds significantly to this body of evidence. The large number of patients, enable us to demonstrate that both azithromycin and roxithromycin have a protective effect. Moreover, we could analyze the effect by duration of treatment, which has clinical implications. An antibiotic stewardship educational point is that once culture results are available, therapy should be optimized for the culprit pathogen. Two days of empiric treatment with macrolides was sufficient to reveal the effect, allowing for discontinuation once microbiological diagnosis was available.

Several RCT investigated optimal treatment for pneumonia. None showed superiority of combination therapy with macrolide versus quinolones. However, some were very small [2, 3, 5], and even the larger ones had few BPP or severe cases. Moreover, the outcome in most studies was clinical stability and not all-cause mortality. The largest RCT compared beta-lactam monotherapy versus beta-lactam-macrolide combination versus quinolones [18]. It included 2283 patients and explored all-cause mortality as the primary outcome. However, in this large study, all patients admitted to the ICU were excluded and mortality was <10%, which may explain the lack of the beneficiary effect of macrolides. This inherent shortcoming of RCT, where the sickest and older adult populations are excluded, preclude deduction of results to these subgroups.

Our study has several limitations. Due to the retrospective nature of the cohort, we did not have data on the severity of patients on admission. Since all patients had BPP, we can assume moderate severity as the minimum, with multi-lobar pneumonia a good proxy for severe disease, as exemplified by their very high mortality rate. Treatment was at the discretion of the treating physician, exposing the data to bias by indication, where treatment is given according to patient severity characteristics, which might influence outcomes. Yet, because the level of macrolide use was not different between patients with lobar pneumonia to those with multi-lobar pneumonia, we believe this potential bias is minimal. Another limitation is that antibiotic therapy data were collected only during hospitalization. Therefore, we were not able to assess the effect of the full course of treatment. However, because diagnoses were available for all patients, the focus of this study was the empirical therapy given. Of note, this study was all in the pre-COVID era, and COVID should not be treated with antibiotics.

In conclusion, in a large cohort of patients with BPP, short duration macrolide therapy, but not quinolones, was protective from in-hospital mortality. The effect was present with azithromycin as well as with roxithromycin. These findings support consideration of therapy with beta-lactam + macrolide combination, for cases of severe pneumonia, unless macrolides are contraindicated.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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