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 (OR 2.040, 95% CI 1.351, 3.083), multi-lobar pneumonia (OR 2.356, 95% CI 1.741, 3.189). Female sex and 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.

Keywords. pneumococcal pneumonia; azithromycin; roxithromycin; mortality.
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 χ² test 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...
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...
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 and 171 received beta-lactam alone. They observed that mortality was lower in patients receiving macrolide plus beta-lactam compared to beta-lactam alone, with an OR of 0.440 (95% CI .254, .764).

### Table 2. Mortality From 72 hours After Admission to Discharge

| Variable         | Alive | Dead | P-value | Alive | Dead | P-value | Alive | Dead | P-value |
|------------------|-------|------|---------|-------|------|---------|-------|------|---------|
| Age (years SD)   |       |      |         |       |      |         |       |      |         |
| No risk          |       |      | <.001   |       |      |         |       |      | <.001   |
| At risk          |       |      | <.001   |       |      |         |       |      | <.001   |
| High risk        |       |      | <.001   |       |      |         |       |      |         |
| Empiric antibiotic|       |      |         |       |      |         |       |      |         |
| Empiric macrolide|       |      | <.001   |       |      |         |       |      | <.001   |
| Duration of macrolide |     |      | <.001   |       |      |         |       |      | <.001   |
| Penicillin       |       |      |         |       |      |         |       |      |         |
| Ceftriaxone      |       |      | <.001   |       |      |         |       |      | <.001   |
| Azithromycin     |       |      |         |       |      |         |       |      |         |
| Roxithromycin    |       |      | <.001   |       |      |         |       |      | <.001   |
| Antibiotic switch|       |      | <.001   |       |      |         |       |      | <.001   |
| 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.
protective effect against mortality, with an OR of 0.4 (95% CI 0.17, 0.92) [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 empirical 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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### 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.
References

1. Metlay JP, Waterer GW, Long AC, et al. Diagnosis and treatment of adults with community-acquired pneumonia. An official clinical practice guideline of the American Thoracic Society and Infectious Diseases Society of America. Am J Respir Crit Care Med 2019; 200: e45–67.

2. Frank E, Liu J, Kinasewitz G, et al. A multicenter, open-label, randomized comparison of levofloxacin and azithromycin plus ceftriaxone in hospitalized adults with moderate to severe community-acquired pneumonia. Clin Ther 2002; 24: 1292–308.

3. Lin TY, Lin SM, Chen HC, et al. An open-label, randomized comparison of levofloxacin and amoxicillin/clavulanate plus clarithromycin for the treatment of hospitalized patients with community-acquired pneumonia. Chang Gung Med J 2007; 30:321–32.

4. Mandell LA, Waterer GW. Empirical therapy of community-acquired pneumonia: advancing evidence or just more doubt? JAMA 2015; 314:396–7.

5. Portier H, Brambilla C, Garre M, Paganin F, Poubeau P, Zuck P. Moxifloxacin monotherapy compared to amoxicillin-clavulanate plus roxithromycin for nonsevere community-acquired pneumonia in adults with risk factors. Eur J Clin Microbiol Infect Dis 2005; 24:367–76.

6. Baddour LM, Yu VL, Klagman KP, et al. Combination antibiotic therapy lowers mortality among severely ill patients with pneumococcal bacteremia. Am J Respir Crit Care Med 2004; 170:440–4.

7. Ceccato A, Cilloniz C, Martin-Loeches I, et al. Effect of combined β-lactam/macrolide therapy on mortality according to the microbial etiology and inflammatory status of patients with community-acquired pneumonia. Chest 2019; 155: 795–804.

8. Lodise TP, Kwa A, Cooler L, Gupta R, Smith RP. Comparison of β-lactam and macrolide combination therapy versus fluoroquinolone monotherapy in hospitalized Veterans Affairs patients with community-acquired pneumonia. Antimicrob Agents Chemother 2007; 51:3977–82.

9. Martin-Loeches I, Lisboa T, Rodriguez A, et al. Combination antibiotic therapy with macrolides improves survival in intubated patients with community-acquired pneumonia. Intensive Care Med 2010; 36:612–20.

10. Metersky ML, Ma A, Houck PM, Bratzler DW. Antibiotics for bacteremic pneumonia: improved outcomes with macrolides but not fluoroquinolones. Chest 2007; 131:466–73.

11. Shorr AF, Simmons J, Hampton N, Micek ST, Kollef MH. Pneumococcal community-acquired pneumonia in the intensive care unit: azithromycin remains protective despite macrolide resistance. Respir Med 2021; 177:106307.

12. Martínez JA, Horcajada JP, Almela M, et al. Addition of a macrolide to a β-lactam-based empirical antibiotic regimen is associated with lower in-hospital mortality for patients with bacteremic pneumococcal pneumonia. Clin Infect Dis 2003; 36:389–95.

13. Domon H, Maekawa T, Yonezawa D, et al. Mechanism of macrolide-induced inhibition of pneumolysin release involves impairment of autolysin release in macrolide-resistant Streptococcus pneumoniae. Antimicrob Agents Chemother 2018; 62:e00161-18.

14. O’Brien ME, Restrepo MI, Martin-Loeches I. Update on the combination effect of macrolide antibiotics in community-acquired pneumonia. Respir Investig 2015; 53:201–9.

15. Reijnders TD, Saris A, Schultz MJ, van der Poll T. Immunomodulation by macrolides: therapeutic potential for critical care. Lancet Respir Med 2020; 8:619–30.

16. Regev-Yochay G, Rahav G, Strahilevitz J, et al. A nationwide surveillance of invasive pneumococcal disease in adults in Israel before an expected effect of PCV7. Vaccine 2013; 31:2387–94.

17. Centers for Disease Control. Pneumococcal Vaccine Timing for Adults. Available at: https://www.cdc.gov/vaccines/vpd/pneumo/downloads/pneumo-vaccine-timing.pdf. Accessed 23 December 2021.

18. Postma DF, Van Werkhoven CH, Van Elden LJ, et al. Antibiotic treatment strategies for community-acquired pneumonia in adults. N Engl J Med 2015; 372: 1312–23.