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Macrolide combination therapy for hospitalized CAP patients? An individualized approach supported by machine learning

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Abstract

Background: The role of macrolide/beta-lactam combination therapy in community-acquired pneumonia (CAP) of moderate severity is a matter of debate. Macrolides expand the coverage to atypical pathogens and attenuate pulmonary inflammation, but have been associated with cardiovascular toxicity and drug interactions. We developed a decision tree based on etiological and clinical parameters, which are available *ex ante* to support a personalized decision pro or con macrolides for the best clinical outcome of the individual patient.

Methods: We employed machine learning in a cross-validation scheme based on a well balanced selection of 4,898 patients after propensity score matching to data available on admission of 6,440 hospitalized patients with moderate severity (non-ICU patients) from the observational, prospective, multinational CAPNETZ study. We aimed to improve the primary outcome of 180 days survival.

Results: We found a simple decision tree of patient characteristics comprising chronic cardiovascular and chronic respiratory co-morbidities as well as leukocyte counts in the respiratory secretion at enrolment. Specifically, we found that patients without cardiovascular or patients with respiratory co-morbidities and high leukocyte counts in the respiratory secretion benefit from macrolide treatment. Patients identified to be treated in compliance with our treatment suggestion had a lower mortality of 27% (OR=1.83, CI = [1.48, 2.27], $P < 0.001$) compared to the observed standard of care.

Conclusion: Stratifying macrolide treatment in patients following a simple treatment rule may lead to considerably reduced mortality in community-acquired pneumonia. A future randomized controlled trial confirming our result is necessary before implementing this rule into the clinical routine.

Introduction

Community-acquired pneumonia (CAP) remains a disease with considerable morbidity and mortality [1-3]. In hospitalized patients with moderate to severe CAP, intra-hospital mortality reaches 14% [4]. Prompt initiation of the correct antimicrobial treatment is essential to prevent unnecessary mortality and complications in patients, particularly in the elderly and other at-risk populations [5]. Macrolides are one of the most frequently used antibiotics and currently widely used in treating a broad range of common bacterial infections including upper and lower respiratory infections [6]. Macrolides can be very effective, as, besides their primary antibiotic effect targeting also atypical pathogens like *Mycoplasma pneumoniae, Legionella ssp.* and *Chlamydia pneumoniae*, they may attenuate inflammation [7, 8]. However, macrolides can be rather ineffective or even detrimental. They may lead to cardiotoxic side-effects in susceptible patients, as several of these agents have been reported to affect arrhythmia-related cardiac effects, including QT interval prolongation, torsades de pointes, ventricular tachycardia and even sudden cardiac death [9]. In addition, they have been associated with serious interactions to co-medication that is frequently used, e.g. statins.

Numerous observational studies, several meta-analyses and two recently well designed randomized and cluster randomized controlled trials have investigated the role of macrolide/beta-lactam *versus* beta-lactam alone in CAP and have revealed conflicting results [10-12]. The RCT by Garin *et al*. enrolling 580 hospitalized CAP patients with a pneumonia severity index between I-IV and with negative legionella urine antigen test on admission found that beta-lactam monotherapy was non-inferior regarding the primary endpoint of early clinical stability. However, a subgroup analysis showed that patients with higher severity (PSI IV) and patients with later on identified mycoplasma infection had a significant benefit from the macrolide combination. Even if for PSI I-III there was no effect, the odds ratio and CI was 1.06 (0.82-1.36), meaning that some patients had a benefit whereas others were harmed. This study nicely illustrates the limitations of such RCTs even for simple questions, since the result of an RCT is based on the average effect that may neither reflect the situation of the individual patient nor the complexity of the underlying factors (e.g. cardiotoxicity *versus* coverage of atypical pathogens). The resulting uncertainty is also reflected by major guidelines suggesting a macrolide/beta-lactam combination for severely ill patients but leaving it at the discretion of the treating physician for patients with moderate CAP.

The competence network for community-acquired pneumonia (CAPNETZ) is an observational, prospective multi-national cohort study [2]. About 12,000 patients from 5 countries with comparable standards of health care (Germany, Switzerland, The Netherlands,

Austria, and Denmark) have been recruited for more than 15 years. The relevant aspects for CAP treatment and management are listed in the database of CAPNETZ including comorbidities and risk factors, clinical check-up results, historical and clinical therapeutic management, pathogen spectrum and resistance, follow-up etc. [13]. We investigated the data of this database by an *ex ante* approach. Without any initial hypotheses about specific patient variables to be associated with treatment benefit, we employed machine learning and identified a simple decision rule consisting of three parameters characterizing the patient on admission.

Methods

Patient population

A detailed description of the CAPNETZ methodology is given elsewhere [2]. Noteworthy, all patients enrolled in the CAPNETZ cohort study had community-acquired pneumonia with at least one of the criteria cough, purulent sputum, history of fever or focal chest signs on auscultation. Patients who had been hospitalized during 28 days preceding the study and patients with severe immunosuppression or with active tuberculosis were excluded. This prospective multicenter study (German Clinical Trials Register: DRKS00005274) was approved by the ethical review board of each participating clinical center (see www.capnetz.de for participating centers). Figure S1 in the Supplementary Material depicts the flowchart for the selection and numbers of the patients. Patients admitted to the ICU on admission or within three days after initial treatment were considered as ICU patients. As, according to major evidence based guidelines, treating ICU patients with a combination therapy of macrolides and β-lactams is mandatory, they were excluded from our study, and 6,440 patients remained.

Data collection

In CAPNETZ, patient information is collected by standardized internet-based data acquisition sheets from 2MT (Ulm, Germany) [2]. Patients' characteristics that describe the health conditions are recorded including smoking history, chronic comorbidities including chronic kidney disease, chronic liver disease, chronic respiratory disease, history of heart insufficiency (in the following "heart insufficiency"), other cardiovascular diseases (in the following "cardiovascular co-morbidity"), cerebrovascular disease, other neurological diseases, diabetes mellitus and former malignancy [2]. Furthermore, data was collected comprising clinical symptoms and signs at the time of admission, observations from radiology, inflammatory parameters and parameters of the severity of the disease. Particularly,

treatment information of each patient was recorded in detail, which included antimicrobial pre-treatment within four weeks before inclusion, initial antimicrobial therapy, change of the antibiotic treatment and reasons for this change [14]. The CAPNETZ database contained 1,190 variables for each patient out of which we assembled those 78 variables for machine learning, which are available at the time of the initial treatment decision. For the decision trees, scale variables were binarized by binning the patients into 20 equally filled quantiles leading to 19 binary variables containing the information if a patient was below the respective quantile or not. Figure S2 shows the flowchart and details for the generation of this assembly. Sputum quality was assessed based on a scheme proposed by Bartlett and coworkers [15].

Definition of treatment and primary outcome: The treatment at admission was defined by the initial antimicrobial therapy. Macrolides (clarithromycin (n=1,923), roxithromycin (n=733), azithromycin (n=101), erythromycin (n=54), and other macrolides (n=14), none got telithromycin) of both, oral and intravenous administration, were included. If not indicated otherwise, we grouped patients treated with these macrolides and a beta-lactam antibiotic as macrolide treated (M-treated), and, if treated only with a beta-lactam antibiotic as non-macrolide treated (nM-treated). If patients were only treated with macrolides, their treatment was denoted as "macrolide mono-therapy". Mortality was assessed at day 28, 30 and 180. [16]. Our primary outcome criterion was death within 180-day after inclusion. Patients who were censored before 180 days after inclusion were considered to be alive (8.0% of the stratified patient population).

Stratifying the patient population employing propensity score matching

Since treatment was not applied by randomization, a propensity score matching was performed to identify a rule based on a balanced cohort. To note, propensity matching excluded survival allowing also the identification of rules containing only a single variable or the rule to always treat with macrolides. Propensity score matching was calculated using Matchit [17] (method=nearest, distance=logit, discard=both, ratio=1:1, caliper=0.2). The caliper parameter was chosen according to the optimal value identified by Austin [18] if scale and binary variables are used. All patient variables were matched for all criteria available on admission and reflecting demographics, disease severity, factors known to be of prognostic relevance (co-morbidities) and blood gas analysis derived lab values (sodium, potassium, glucose, lactate) that are usually available on admission. Scale variables and their squares were z-normalized, binary variables were used unchanged (0, 1). The result of Matchit provided a balanced cohort of 2,449 M and 2,449 nM treated patients. To estimate the balance between treated and non-treated patients after propensity matching, z-differences were calculated for each variable. In well-balanced data, the z-difference should follow a

normal distribution (mean zero, σ=1), i.e. ≥95% of all observed values are in [-2σ, 2σ] [19]. All results from machine learning base on the cohort of these propensity matched patients.

Furthermore, for each leaf of the tree representing our rule, an additional propensity matching was done. By this, balancing of patients, who have been treated in compliance *versus* patients who have not been treated in compliance to our rule was enforced. If not mentioned otherwise, we used this propensity matching for every leaf for all displayed results of our rule. For the leaves of all stumps, we used Matchit with the option caliper=0.2 as described above. For the leaves of the trees (depth 2), this was not necessary. Instead, for a leave with low patient numbers (~ less than 100, which occurred often for condition δ, sometimes for condition β and rarely for conditions α and γ in Figure 1), the number of variables exceeded the number of patients, which caused numerical problems. In these cases, we reduced the number of balancing variables to those having the highest z-difference before matching and used the maximal number of variables with which no numerical problems occurred. After removing all patients with missing values (see next section), n=2,244 patients were included, and after propensity matching of all leaves, n=1,826. In particular, for only 2,340 patients of the initial 6,440 patients the variable leukocyte counts in the respiratory secretion was available. For calculating the performance of our rule when considering the sputum quality, only patients with good sputum quality (n=1,386) were selected.

Rationale of the machine learning approach

First, we aimed to estimate the impact on the mortality for each single patient variable in CAPNETZ used for the treatment decision to apply combined macrolide treatment. For this, we tested all variables directly as a rule for macrolide treatment. Patients with missing values (NaN) for the tested variable were removed. For each scale variable, every of the 20 split points from binarization (see section "Data collection") was tested and the one with the optimal odds ratio selected. Figure S2 depicts the flowchart of the assembly of the patient characteristics. For each treatment rule, the improvement of survival was estimated by the odds ratio and reduced death rate. The death rate in a subgroup was calculated by the number of non-survivors divided by the total number of patients in the subgroup. To note, this analysis didn't base on a cross validation scheme, and hence these odds ratios may be overestimated. To identify a more effective, but still robust rule, we combined a maximum of three variables in a decision tree of depths two containing a maximum of three nodes. A prototype of such a tree is sketched in Figure S3a. We calculated the odds ratio for every possible combination of variables for such a tree. Figure S3b illustrates such combinations

exemplarily for three binary variables. To note, the total number of combinations for such trees is about n=4*10^8 but using intelligent enumeration the best tree for a given set of patient samples can be identified in reasonable computational time. To overcome overfitting, we applied a cross-validation scheme. After propensity matching of M-treated and nM-treated patients, we randomly partitioned the patient cohort into 100 parts with equal numbers of patients, and selected the best decision tree based on 99 parts. The selected tree was validated by calculating the odds ratio for this tree based on the patients of the remaining partition. This was repeated 100 times considering each part as the validation set. Finally after assembling the results of all 100 validation sets, patients with at least one missing value in any of the variables which were relevant for the decision, were not considered. In addition for the result propensity matching was renewed balancing M- and nM-treated patients in every leave of the tree separately.

Statistical testing

For scale variables, statistical testing for differences in the distributions of the patient variables was performed performing a Mann-Whitney test, and for binary variables a Fisher's exact test, followed by multiple testing correction [20]. P-values for the mortality rates were not corrected for multiple testing. P-value and confidence interval calculation of the confusion matrices for the odds ratios were based on the R function oddsratio from the “fmsb” package. Kaplan Meier analysis was performed using the R functions survfit from the package “survival” and ggsurvplot from the package “survminer”. For the Cox-Hazard regression analysis, we used the function coxph of the R package “survival” (default settings). As survival object we used the complete survival information until day 180.

Odds ratios (OR) were calculated to compare the survival rate of patients that were treated according to the rule with patients that were treated against the recommendation of the rule.

Results

General characteristics of the study population

Between October 2002 and June 2017, a total of 11,818 adult patients from 25 clinical centers with proven CAP were enrolled by CAPNETZ. Hospitalized patients not in the ICU and patients who received either a macrolide/beta-lactam combination therapy or received only a beta-lactam were selected for our study population. In the following, they are denoted as “M-treated patients” (macrolides-treated patients, n=2,777, and “nM-treated patients” (non-macrolides-treated patients, n=3,663) (Figure S1). Table 1 shows the averaged values of the most relevant variables, and variables which were significantly different between M-

treated and nM-treated patients. In summary, M-treated patients had a better survival, which, in summary, is most likely explained by younger age, less co-morbidities and a lower CAP severity rather than the treatment itself.

Balancing the patient cohorts

In the initial patient cohort, we observed comparably large differences in critical variables between M- and nM-treated patients, in particular age, co-morbidities, severity, inflammatory markers and mortality. To identify clinically usable prognostic variables, we adjusted for all variables and assembled a well-balanced cohort of 4,898 patients by matching each patient, who received macrolides with a patient who didn't receive macrolides (1:1) with same propensity in all variables. The variables are listed in Table S1 (from all patients, before balancing) and Table S2 (from the matched patients). Mortality was not part of this list. Z-differences between the groups were calculated and the balance estimated by performing a statistical test for each variable. Despite patients were not matched for mortality, the balanced cohort did not reveal a relevant nor significant difference in mortality (see below). The z-differences of 95% of the listed variables were in the 2σ region, indicating that the data was well-balanced (Table S2). This balanced cohort was used in the next sections.

Evaluating each single patient variable as a rule for treatment decision

We first investigated each individual patient variable to suit as a rule for the decision to apply macrolides as the initial antimicrobial treatment. The best performing variables are shown in Table 2. In contrast to the unbalanced cohort, we didn't observe a noteworthy difference in survival between M- and nM-treated patients (OR=1.06, 180 days mortality: 7.64% and 8.08% of M- and nM-treated patients, respectively). The most powerful single variable to identify patients who benefit from macrolide treatment was high or medium leukocyte counts in the respiratory secretion, followed by non-elevated blood pressure, elevated severity score and absence of cardiovascular co-morbidities (i.e. coronary heart disease, hypertension, heart valve defect, cardiomyopathy and arrhythmia). Noteworthy, chronic heart insufficiency, which can exacerbate during pneumonia, is documented additionally as an individual variable in the CAPNETZ electronic CRF. Furthermore, patients with no chronic respiratory diseases, a high leukocyte count in the blood and a higher CRB65 benefitted from macrolide treatment.

Identifying a decision tree

To obtain a robust decision rule with an optimal odds ratio, we performed machine learning with level 2 decision trees. Each run of a 100-fold cross-validation resulted in the tree of Figure 1 to be optimal with an OR of 1.83, where patients with missing values for respiratory secretion (60%) where assigned to the “low leukocytes” group. After removing these patients

the overall odds-ratio from the cross-validation results even increased to OR=2.34, CI = [1.56, 3.51], P < 0.001, n=1,826. This corresponds to an overall death rate of 3.94%, and a decrease of mortality by 37.9% of patients identified to be in compliance to the rule compared to the original death rate of 6.35%. Since we had to exclude patients with missing values in any of the three variables, the original death rate of these patients differed from all patients of the balanced cohort in Table 1. A Kaplan-Meier analyses accounting for censored data and the time dependent outcome confirmed the distinct benefit in survival (P < 0.001, Figure S4). Applying a Cox-hazard regression model to our rule yielded a hazard ratio of 0.45 (CI = [0.31, 0.67], P < 0.001). We investigated if the sputum quality affected the application of our rule. This was not the case. If we included only patients with good sputum quality, we got comparable results (OR=2.44, CI = [1.51, 3.95], P < 0.001, n=1,386). Next, we investigated if the rule was influenced by the detection of an underlying pathogen (either in the blood, sputum, BAL, respiratory secretion or aspirate). For these patients, the odds ratio was considerably higher (OR=3.55, CI = [1.57, 8.04], P= 0.001, n=438). In patients in whom a pathogen was either not found or the test was not performed, the odds ratio was lower, but still significant (OR=1.90, CI = [1.14, 3.17], P=0.013, n=1,182). To note, we observed that M-treated patients showed a tendency of better survival compared to nM-treated patients, however this was not significant (OR=1.34, CI =[0.920, 1.97], P=n.s.).

In condition (γ) of Figure 1, patients had a respiratory disease and medium or high leukocyte counts in the respiratory secretion. If, in addition, a patient also had a cardiac comorbidity, the rule to treat with macrolides increased the odds ratio for survival considerably (OR=8.01, CI = [1.77, 36.3], P = 0.002, n=194), but note that this amendment to the rule does not base on a cross-validation scheme.

Then, our rule was applied separately to patients treated with macrolide monotherapy and matched controls (treated with beta-lactam). We observed a high odds ratio for patients with macrolide monotherapy but due to low patient number (n=52) this was not significant (OR=4.20, CI = [0.421, 41.9]). Next, we investigated how the rule performed among subgroups of patients treated with the same macrolides (613 clarithromycin, 246 roxithromycin, 44 azithromycin and 7 erythromycin treated patients) and their propensity matched nM-treated controls. We observed a similar odds ratios for clarithromycin (OR=2.36, CI= [1.46, 3.84], P<0.001). For roxithromycin, we observed a lower odds ratio (OR=1.98, CI= [0.899, 4.34], P=n.s.). A benefit for survival was not significant for roxithromycin, which, however, may be not only due to a less favorable efficacy/safety profile, but also the lower number of patients in this subgroup. For erythromycin and azithromycin, the patient numbers were too low to draw any conclusions. Odds ratios with confidence intervals and survival

rates are given in Table S3 a). Table S3 b) lists the odds ratios and survival rates for the according patient groups if always macrolides were applied.

As described in Methods, patients were excluded which were admitted to the ICU within the first three days after initial treatment. Including these patients would have misled the machine learning algorithm as most of these patients would have received combination therapy even if they were initially treated with a beta-lactam monotherapy. Still, it is reasonable to observe how our rule performed when we also included patients, who were initially admitted to the regular ward but transferred to the ICU within the next 3 days. However, this didn't change the results (OR=2.24, CI = [1.49, 3.37], $P < 0.001$).

We also analyzed how the rule performed among patients treated with other antibiotics. Using our rule in patients treated with macrolide beta-lactam combination therapy *versus* fluoroquinolones (either mono-therapy or combined with a beta lactam) did not reveal significant survival differences. Other comparisons didn't yield meaningful results due to too low patient numbers.

Discussion

Testing each patient variable on its own as a single rule, we identified in particular elevated leucocyte count in sputum but also the following *ex ante* parameters as variables predicting a benefit from macrolide treatment: absence of cardiovascular co-morbidities as well as non-elevated blood pressure and increased CRB65. The first and the last factor reflect increased inflammation. By testing all combinations of all variables, machine learning came up with the following rule: treat the patient with macrolides if the patient has no chronic respiratory disease and no cardiovascular co-morbidity, or, if the patient has a chronic respiratory disease and shows high or medium leukocyte counts in the respiratory secretion. We rationalize this rule in the following.

Patients with cardiovascular co-morbidities including coronary artery disease, hypertension, heart valve defect, cardiomyopathy and prior arrhythmia are at increased risk for macrolide induced QT interval prolongation, ventricular tachycardia, ventricular fibrillation, torsades de pointes and even sudden cardiac death [9, 21-24]. We saw in our data that macrolides had already been intentionally less applied to patients with heart insufficiency. In contrast, such a difference was not observed for patients with the other, above listed cardiovascular co-morbidities. According to our study, macrolides should not only be avoided in patients with heart insufficiency, but particularly in patients with (other) cardiovascular co-morbidities. To note, combining the patient variables heart insufficiency and cardiovascular co-morbidities

did not improve the performance of our rule. According to our observations, patients with elevated leukocyte counts in blood and the respiratory secretion benefit from macrolide therapy, which may be explained by the known anti-inflammatory effect of macrolides. In line, a recent monocentric prospective cohort study revealed that only patients with high inflammatory response and pneumococcal CAP had a benefit from macrolide/beta-lactam combination therapy (adjusted OR: 0.28; 95% CI, 0.09-0.93). To obtain the rule, microbiological etiology was not considered, since we used only parameters that are available at initial patient assessment. Still, assessing the data from the microbiological diagnosis showed that patients in whom a pathogen was detected would benefit more from the use of our rule than patients in whom no pathogen was detected.

Patients with bronchiolitis obliterans syndrome after lung transplantation particularly benefit from macrolide therapy, if they exhibit an increased BALF neutrophil count [25]. A recent systematic review found that the most frequently reported effects of macrolides in clinical studies were a decrease in the number of neutrophils and the concentrations of neutrophil elastase as well as of several pro-inflammatory cytokines [26].

Regarding respiratory co-morbidities, the rule partitions the patient cohort into two arms. To get the complete picture, we discuss both arms:

> (1) If a patient is *not* having a chronic respiratory disease *and* is not having a cardiovascular co-morbidity, then the rule recommends applying macrolides.
>
> (2) If a patient is having a chronic respiratory disease, macrolides should be applied if leukocyte levels are elevated in the patient's respiratory secretion.

We first discuss arm (1). “Respiratory co-morbidities” summarizes COPD, bronchial asthma, lung fibrosis, bronchiectasis, former bronchial carcinoma, sarcoidosis, silicosis, asbestosis, exogenous allergic alveolitis, sleep apnea and pulmonary hypertension. In this arm, patients should be treated with macrolides only if they have neither a chronic respiratory nor a cardiovascular co-morbidity, otherwise not. It is known that COPD can be associated with chronic heart diseases due to smoking as the common risk factor [27]. Indeed, in our patients we observed a highly significant correlation of these co-morbidities ($P<0.001$, Fisher's exact test) suggesting that a “chronic respiratory disease” may point to a cardiovascular co-morbidity, which may have not been detected so far coping for false negatives. Furthermore, patients with both, cardiovascular and respiratory co-morbidities, tend to be older (average age of patients with and without cardiovascular comorbidities: 73.3 and 58.4, respectively, $P< 0.001$; average age of patients with and without respiratory comorbidities: 68.0 and 61.5, respectively, $P< 0.001$) and it is known that the most frequent atypical pathogen,

Mycoplasma pneumoniae, affects primarily younger patients [28, 29]. Therefore, patients with these co-morbidities may have a reduced benefit, regarding the extended spectrum of macrolides. Regarding arm (2), macrolides are known to attenuate pulmonary inflammation in patients with a variety of lung diseases such as bronchiolitis, cystic fibrosis, non-CF bronchiectasias, and they reduce exacerbation rates in COPD [30, 31]. Following our rule in this arm, we suggest to only treat these patients with macrolides if elevated leukocyte levels in the patient's respiratory secretion are found. Notably, “Elevated leukocytes in sputum” was the patient variable with the most impact as a single rule. It is reasonable, that macrolides are beneficial when treating an acute respiratory disease with elevated leukocytes levels in the respiratory secretion, as they are known for their anti-inflammatory effects, which are probably conferred by attenuating neutrophil influx into lung parenchyma [7]. Sputum microscopy, which could in theory be performed as point of care test, has been considered a standard procedure for many years and was typically preformed by microbiologist in order to decide if the quality of the sample justifies further culture analysis. However, due to its labor intensity - it requires homogenization of the sample compared to a simple blood smear [32] – its current use is limited to microbiological labs. Therefore the result may not always be available on the day of admission. Yet, automated devices for point of care sputum analysis are currently under development [33].

It is not only important to treat patients with macrolides who will most likely benefit from it, but also to withhold treatment when the risk outweighs the potential benefit. The odds ratio for survival for the rule "always give macrolides" was considerably lower than for our rule. To further explore the underlying mechanism by which macrolides increase mortality, we discuss the patient variable cardiovascular co-morbidity. From a clinical perspective, life-threatening arrhythmias are the most likely cause of macrolide induced mortality. However, the hazard of a non-observed cardiac arrest due to arrhythmia is highest on the regular ward, where patients –in contrast to the ICU- are not monitored. Indeed, we observed a significantly higher death rate of macrolide treated patients compared to patients without cardiovascular co-morbidities at non-ICU units, which we didn't observe for patients at the ICU (n=134 *versus* n=89 non-survived patients at non-ICU units with and without cardiovascular co-morbidity, n=6 *versus* n=12 non-survived patients at the ICU with and without cardiovascular comorbidity, respectively, P=0.025 employing a Fisher's exact test). A smaller fraction of the investigated patients received azithromycin as initial antimicrobial treatment. Azithromycin is one of the novel macrolides and considered as a macrolide with reduced cardiac toxicity and a decreased potential for drug interactions [34]. However, the American Food and Drug Association strengthened their warnings and precautions of azithromycin from 2013 about its risk of potentially fatal heart rhythms [21]. Also Ray *et al.*

[23] showed the cardiotoxic potential of azithromycin in susceptible patients. Excluding these patients didn't change the results (data not shown). In turn, erythromycin and clarithromycin are reported to interact with theophylline, carbamazepine and terfenadine, while there is no similar report for azithromycin [8, 35, 36]. Considering the distinct profile of azithromycin, it may be studied separately observing a reasonable large patient cohort.

Limitations and strengths

The limitation of our study is the observational, not randomized design. Even if intended, not all consecutive CAP patients are enrolled into CAPNETZ. This may inflict a bias that may reduce external validity. This also applies to the variable “elevated leucocytes in sputum”: Even if national recommendations require sputum analysis within 2-4 hours after sampling, it cannot be excluded, that this time was exceeded for some samples.

We observed considerable differences in important patient variables of M-treated and nM-treated patients and needed to balance these employing propensity score matching. “Hence, to clearly evidence our rule, a randomized controlled trial is necessary. The strengths of our study are that our analysis bases on a very large and well-phenotyped cohort, and that our analysis focused on simple decision trees employing cross-validation avoiding overfitting very likely leading to a robust result, and the obtained algorithm is biological plausible.

Conclusion

Investigating a well-balanced very large cohort from the CAPNETZ study group employing machine learning, we identified a rule for combined macrolide treatment comprising chronic cardiovascular and chronic respiratory co-morbidities as well as leukocyte counts in the respiratory secretion at admission. Since this was not a hypothesis driven approach, it is to us very reassuring that machine learning came up with parameters that indeed reflect the advantages and disadvantages of macrolides, i.e. a benefit for patients with high pulmonary inflammation and a possible hazard in patients with cardiovascular co-morbidities. Clinicians are well aware of macrolide risks and benefits. However, it is difficult to make an optimal decision for an individual patient, in particular with a high inflammatory load, a moderate disease severity and cardiovascular co-morbidity – a frequent patient phenotype in CAP. Here the rule helps by prioritizing the different decision levels and weighting clearly structured risks against benefits. The rule suggests considerable reduction of the mortality rate 180 days after admission. This rule may be a step towards personalized treatment

decisions but requires prove by a randomized controlled trial.

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Table 1. Comparison of clinical characteristics and mortality between hospitalized patients (not in the ICU) treated with macrolides (M-treated, macrolide combination therapy) and not treated with macrolides (nM-treated)

Variable	Initial cohort[1]			Balanced cohort[1,2]	
	M-treated patients (N = 2,777)	nM-treated patients (N = 3,663)	Significance of the difference (corrected)	M-treated patients (N = 2,449)	nM-treated patients (N = 2,449)
Age in years	62.6 ± 18.0	66.7 ± 17.1	<0.001	63.2 ± 17.7	63.9 ± 17.5
Male gender	61.3	59.4	n.s.	60.6	61.5
Current smoker	32.2	25.1	<0.001	30.9	29.3
Nursing home resident	3.85	12.5	<0.001	4.37	4.53
Confusion	7.30	15.7	<0.001	7.8	7.7
Enteral nutrition	3.0	4.7	0.024	3.0	2.6
Vaccination against influenza within the last 12 months	38.0	43.8	<0.001	38.1	38.3
Comorbidities					
Former malignancy	9.9	12.0	n.s.	10.0	11.0
Chronic respiratory disease[3]	36.9	39.0	n.s.	37.2	37.2
Chronic kidney disease	11.7	13.2	n.s.	11.6	11.2
Chronic liver disease	3.4	3.8	n.s.	3.4	3.1
Cerebrovascular disease	7.6	17.7	<0.001	8.3	7.9
Other neurological disease[4]	5.5	11.2	<0.001	6.1	6.0
Diabetes mellitus	20.8	21.7	n.s.	20.9	20.4

Heart insufficiency	18.7	27.1	<0.001	19.8	21.5
Other chronic cardiovascular disease[5]	38.8	40.0	n.s.	38.9	38.5
Symptoms at time of presentation					
Cough	90.4	86.8	<0.001	89.8	89.4
Purulent sputum	55.5	49.9	<0.001	45.5	47.2
Fever	33.2	32.7	n.s.	32.5	32.4
Clinical observations					
Positive focal auscultation sign	80.3	77.5	n.s.	79.8	79.7
Oxygen saturation (%)	92.7 ± 5.0	93.2 ± 4.0	n.s.	92.8 ± 4.9	93.0 ± 4.3
Radiological observations					
Multilobular infiltrate	14.4	13.0	n.s.	14.5	14.9
Pleural effusion	20.9	19.8	n.s.	20.7	20.2
High or medium leukocyte counts in the respiratory secretion	29.9	22.6	<0.001	28.2	27.7
Blood parameters and clinical chemistry					
C-reactive protein (mg/L)	151 ± 120	127 ± 115	<0.001	146 ± 120	138 ± 117
Thrombocytes (G/l)	252 ± 108	259 ± 110	0.036	254 ± 110	255 ± 109
Urea (mg/dL)	6.94 ± 5.06	7.61 ± 5.51	<0.001	7.02 ± 5.15	6.99 ± 4.98
Severity parameters and mortality					
CRB-65 > 1.75	21.4	29.5	<0.001	21.8	22.2
CRB-65 score	0.964 ±0.800	1.14 ±0.883	<0.001	0.970 ±0.805	0.971 ±0.803
CRB score	0.423±0.594	0.506±0.678	0.0068	0.420±0.595	0.408±0.592
30-day mortality	3.6	5.7	0.0087	3.8	3.4
180-day mortality	7.2	11.6	<0.001	7.6	8.1

[1] Data are presented as percentages or mean ± standard deviation. All the values were obtained from preprocessed data (after missing value replacement).

[2] Balanced cohort after propensity matching

[3] Chronic respiratory disease included COPD, asthma, lung fibrosis, bronchiectasis, bronchial carcinoma, sarcoidosis, silicosis, asbestosis, exogenous allergic alveolitis, sleeping apnoea and pulmonary hypertension.

[4] Other neurological disease included epilepsy, restless legs syndrome, Parkinson's disease, dementia and multiple sclerosis, hemiparesis band polyneuropathy.

[5] Other chronic cardiovascular diseases included coronary heart disease, hypertension, heart valve defect, cardiomyopathy and arrhythmia.

[6] Missing values in the CRB 65 score were treated to be 0.5. Since the thresholds are computed as mean of two consecutive scores, values of a multiple of 0.25 are possible.

Table 2. Best performing single variables

	OR[1]	Confidence interval	P-value	Compliant death rate[2]	Non-compliant death rate[3]	Rate of macrolide treatment[4]
Always apply macrolides	1.06	0.864, 1.31	n.s.	0.0764	0.0808	1
Leukocyte counts ⩾ 10 per visual field	2.07	1.38, 3.1	<0.001	0.0466	0.0919	0.752
Diastolic blood pressure < 60 mmHg	1.4	1.14, 1.71	0.0013	0.0711	0.0965	0.212
CRB65 > 1.25[5]	1.28	1.03, 1.59	0.025	0.0695	0.0873	0.232
CRB > 0.25[5]	1.27	1.03, 1.57	0.027	0.0714	0.089	0.368
Systolic blood pressure < 135 mmHg	1.26	1.02, 1.56	0.034	0.0699	0.0866	0.616
No cardiovascular disease[6]	1.25	1.01, 1.55	0.039	0.0708	0.0872	0.62
BMI < 29.7	1.25	1.01, 1.54	0.044	0.0704	0.0862	0.802

[1] OR: Odds ratio

[2] Death rate of patients who were treated in compliance with the treatment rule

[3] Death rate of patients who were treated in against the treatment rule

[4] Ratio of patients who were treated with macrolides and who were in compliance to the rule. It reflects the limitation of the rule to a small group of patients if this rate is far different from 50%

[5] Missing values in the CRB or CRB65 score were treated to be 0.5. Since the thresholds are computed as mean of two consecutive scores, values of a multiple of 0.25 are possible.

[6] Other chronic cardiovascular diseases included coronary heart disease, hypertension, heart valve defect, cardiomyopathy and arrhythmia.

Figure legends

Figure 1. The identified treatment rule depicted as a decision tree.

Treating a CAP patient with macrolides is suggested if either (i) the patient has no chronic respiratory disease *and* no cardiovascular co-morbidity (left hand site of the figure), or, (ii) if the patient has a chronic respiratory disease *and* shows high or medium leukocyte counts in the respiratory secretion (right hand site of the figure). The rule is now explained for each condition:

Condition (α): 60% of the patients (n=1,196) had no chronic respiratory disease. Of these, n=724 patients had no cardiovascular comorbidity. For these patients, the rule suggests macrolide treatment. In condition (α), n=696 patients survived if treated according to this rule, n=28 died.

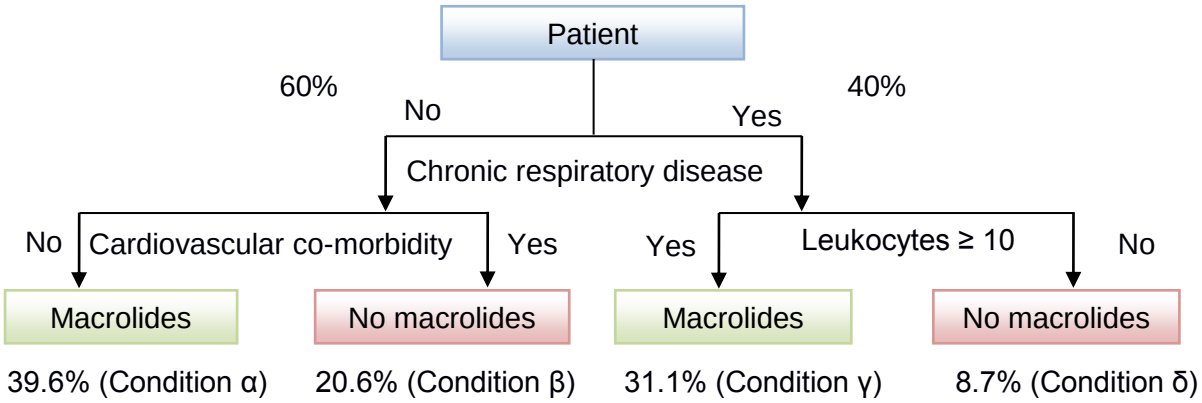
Condition (β): If a patient had no chronic respiratory disease, but a cardiovascular comorbidity, the rule suggests no macrolide treatment. This condition was found in n=376 patients. In condition (β), n=335 patients survived if treated according to this rule, n=41 died.

Condition (γ): 40% of the patients (n=730) had a chronic respiratory disease. The rule suggests macrolide treatment, if the leukocyte counts in the respiratory secretion of these patients is medium or high. This condition was found in n=568 patients. In condition (γ), n=532 patients survived if treated according to this rule, n=36 died.

Condition (δ): If a patient had a chronic respiratory disease and the leukocyte counts in the respiratory secretion was low, the rule suggests no macrolide treatment. This condition was found in n=158 patients. n=147 patients survived if treated according to this rule, n=11 died.

Leukocytes ≥ 10: Leukocytes in the respiratory secretion ≥ 10 per visual field (object 10×, ocular 10×). Leukocytes ≥ 10 is regarded as middle or high. The given percentages refer to the subgroup of the balanced cohort with no missing value in any of the variables being relevant for the respective patient.

Figure 1



	Condition α		Condition β		Condition γ		Condition δ	
	Survived	Died	Survived	Died	Survived	Died	Survived	Died
M-treated	**354**	**8**	**165**	**23**	**275**	**9**	**69**	**10**
nM-treated	**342**	**20**	**170**	**18**	**257**	**27**	**78**	**1**

In compliance with the rule

Not in compliance with the rule

Supplementary Material

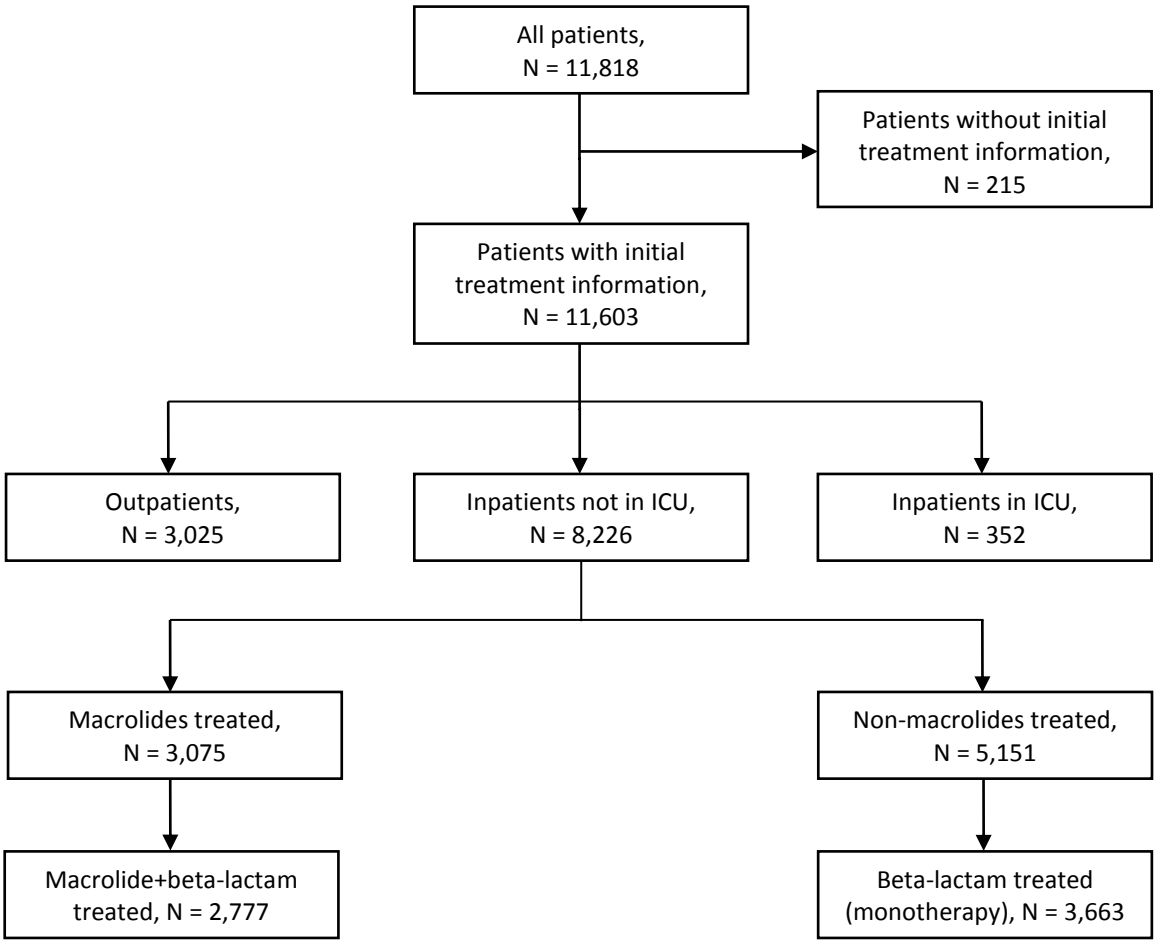


Figure S1. Flowchart of the patient selection

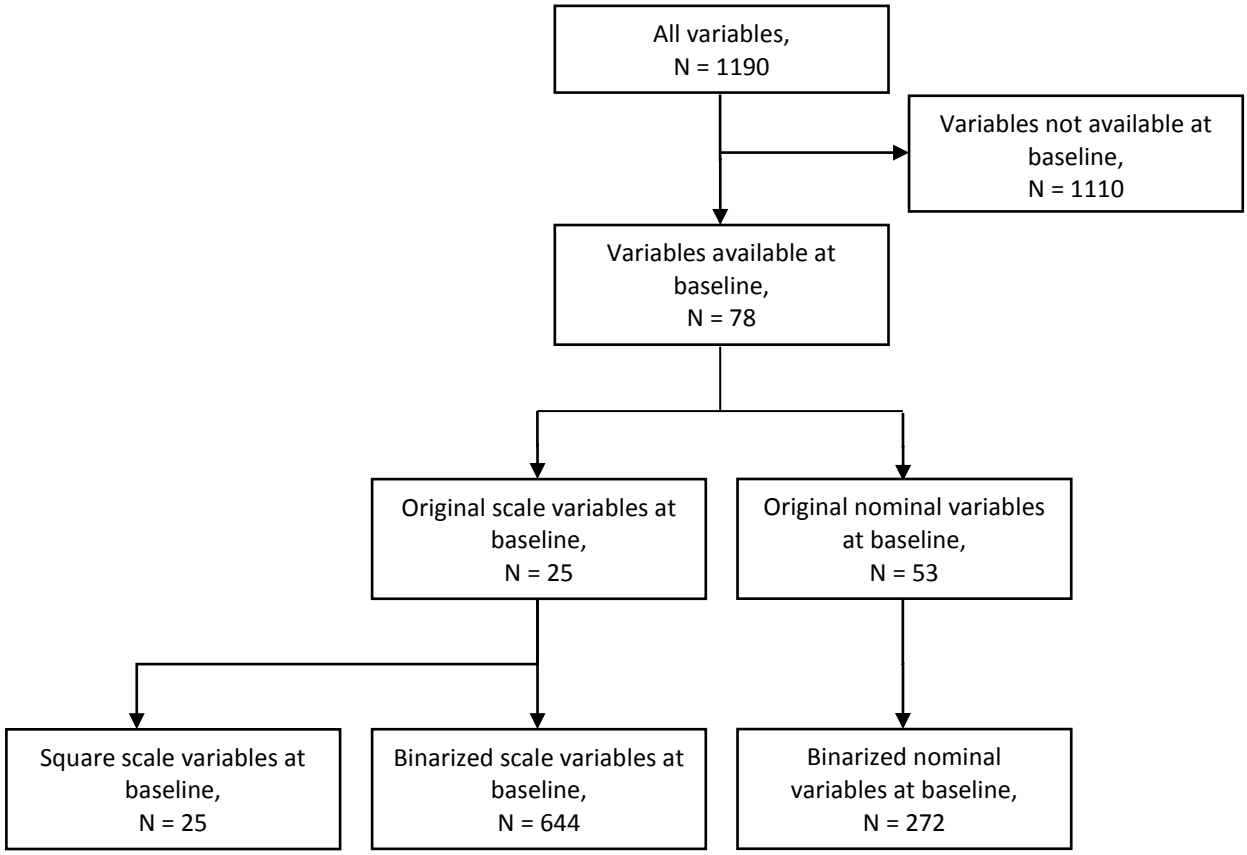
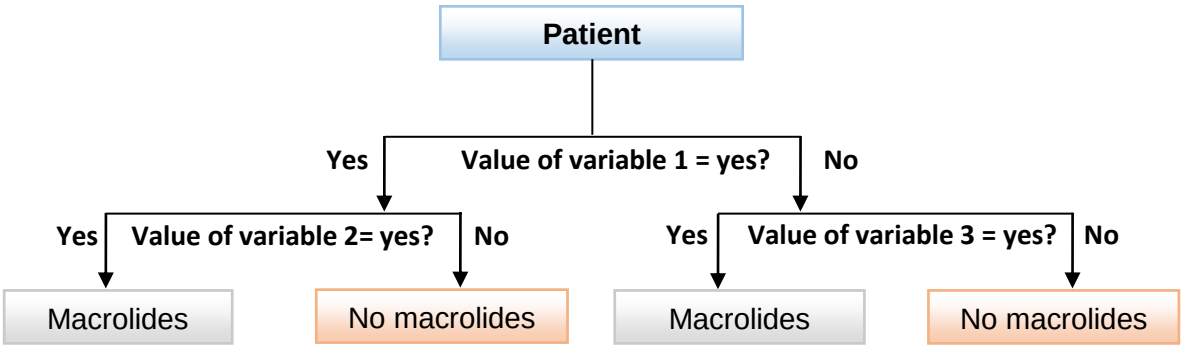


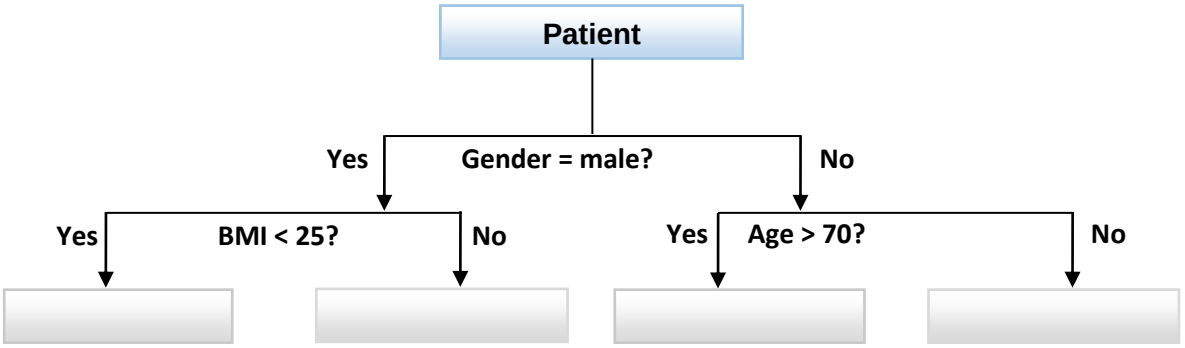
Figure S2. Flowchart of the assembly of the patient characteristics

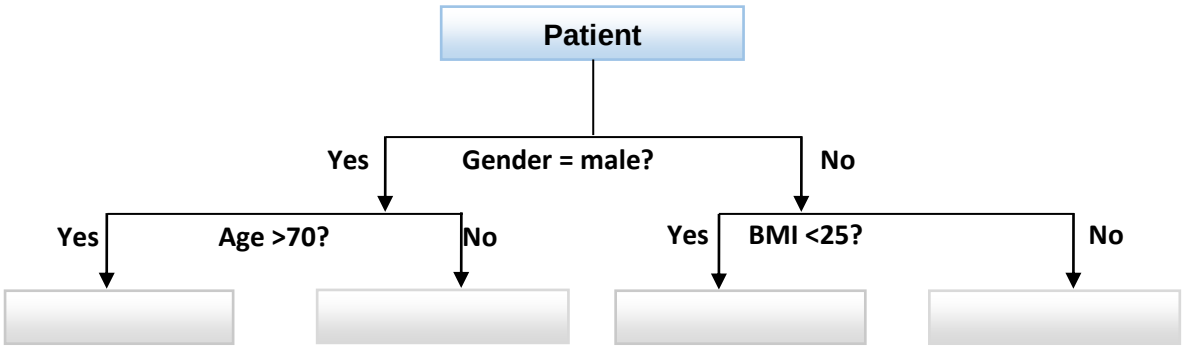
The CAPNETZ database contained 1,190 variables for each patient from which in total we assembled 916 binary variables for machine learning and 187 variables for propensity matching. Nominal variables with more than 90% of missing values (NaN) and scale variables with more than 50% NaN were removed. Non-relevant variables (e.g birth place of the patients) were removed. Furthermore, variables with 99% or more unique values were removed. Noteworthy, antimicrobial pre-treatment within four weeks before inclusion was considered as a patient variable. Of the remaining variables, we selected 78 baseline variables, which values were available at the time of the initial treatment decision. It consisted of 25 scale variables and 53 nominal variables. In addition, we generated nominal variables for the severity scores CRB, CURB, CRB-65 and CURB-65 from the given information from the database. Any fulfilled criterion scored +1, any non-fulfilled criterion scored +0, and any unknown criterion scored +0.5. Missing values in the scale variables were replaced by the median of all values for this variable. Missing values of nominal variables were replaced by the category "NaN". For the decision trees, these variables needed to be binarized. Scale variables were binarized by binning the patients into 20 equally filled quantiles (5% quantile steps) of the whole data leading to 19 new binary variables containing the information if a patient was below the respective quantile or not. In case the scale variable had n < 20 different values (e.g. CRB65) we took these values as quantiles. Nominal variables typically contained two values (e.g. cough at admission = "yes" or "no") and the may have contained the value "NaN" if data was missing for a certain patient. Nominal variables with n values were binarized into $2^{n-1}-1$ binary variables including every possible combination of the n values and 2^n-1 if there were entries with "NaN". For the propensity score method, we used in addition the square of the scale variables in order to balance the variance of these variables, too. Binary variables with very low information entropy (more than 99% of the patients had the same value) were removed.

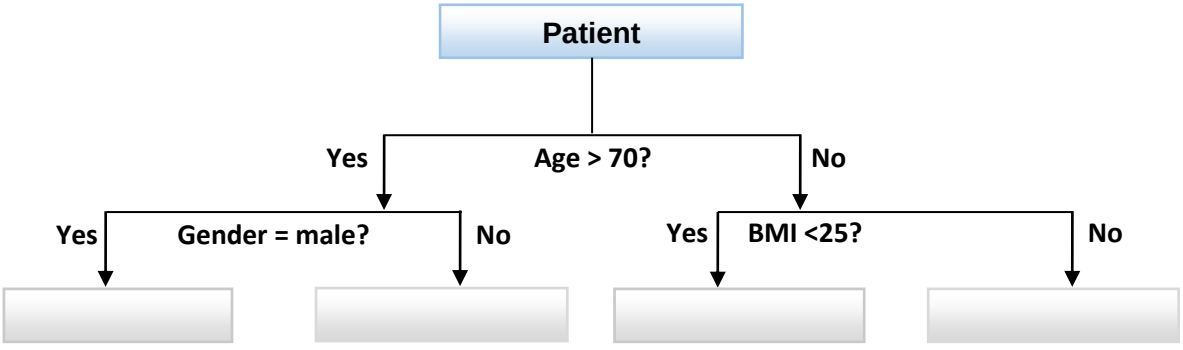
Besides this, for propensity scoring, all patient variables with information which was available at admission were used, hence mortality was not used for propensity scoring.



a)







b)

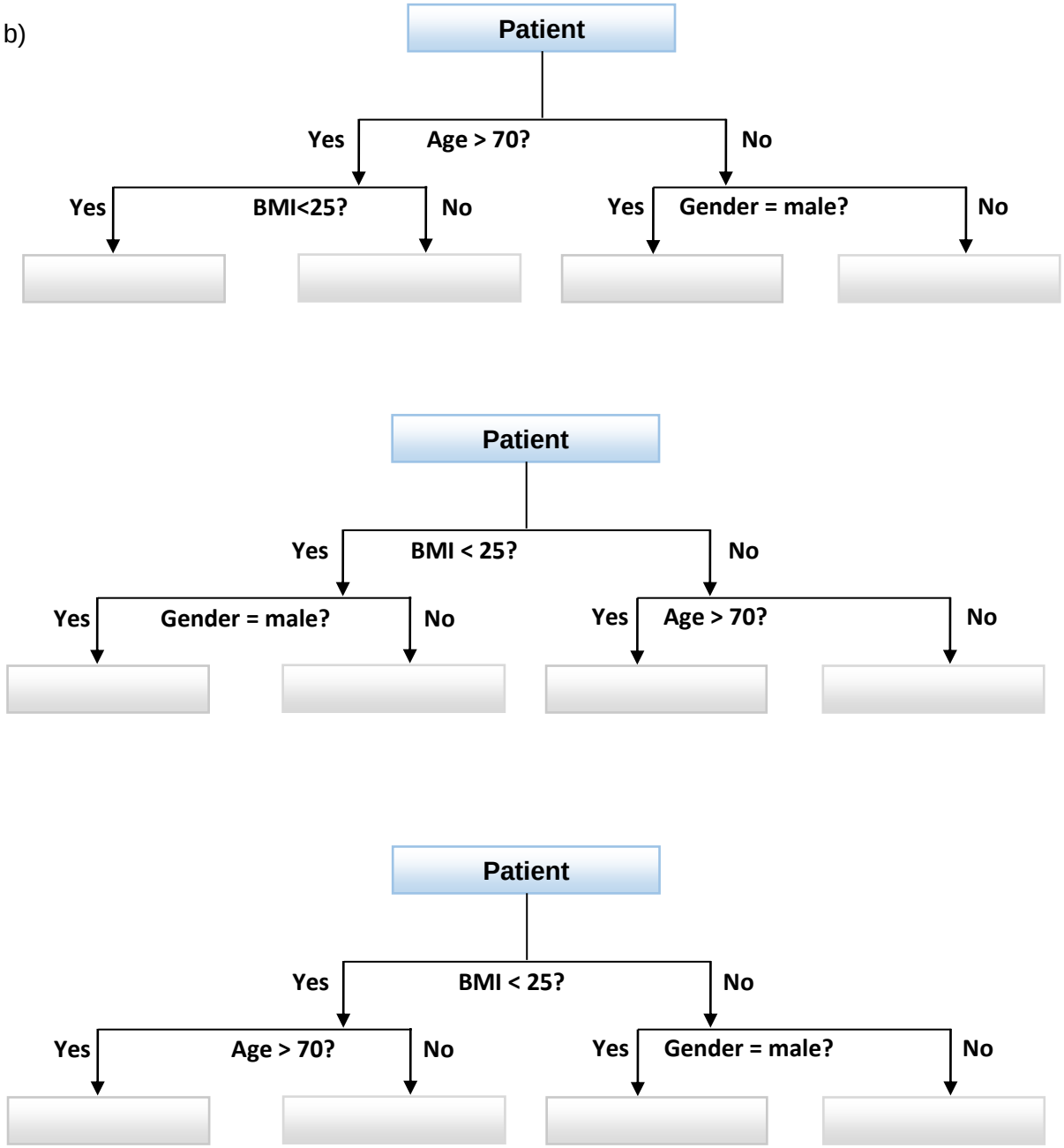


Figure S3. a) A prototype of a decision tree of depth 2 consisting of three nodes (variables 1, 2 and 3). b) All possible combinations of the three variables gender, age>70 and BMI<25. The leaves of the trees in Figure S3b are then labelled (macrolides, no macrolides) according to be best odds ratio.

Table S1. Patient variables of M treated and nM treated patients of the initial cohort

	Mean M-treated[1]	Standard deviation M-treated	Mean nM-treated	Standard deviation nM-treated	z-Difference	P-value	P-value (corrected)
Scale variables							
BMI	26.1	5.62	26	5.53	0.886	n.s.	n.s.
Systolic blood pressure (mmHg)	131	22.5	131	23.9	0.108	n.s.	n.s.
Diastolic blood pressure, (mmHg)	74.2	13.1	74.6	13.6	-1.25	n.s.	n.s.
Heart frequency (/min)	92.8	18.9	92.6	18.9	0.375	n.s.	n.s.
Breath rate (/min)	21.4	5.64	21.3	6.07	0.98	n.s.	n.s.
Temperature (^{0}C)	37.9	1.15	37.9	1.11	0.696	n.s.	n.s.
Leukocytes (/nL)	13.2	5.85	13.4	6.13	-1.46	n.s.	n.s.
Hemoglobin (mmol/L)	8.18	1.15	8.16	1.35	0.656	n.s.	n.s.
Haematokrit (%)	38.8	5.04	39	5.11	-1.49	n.s.	n.s.
Thrombocytes (/nL)	252	108	259	110	-2.71	<0.001	0.0358
Average liter O_2 suppl. in ventilation during arterial blood gas analysis	0.593	1.44	0.662	2.17	-1.52	n.s.	n.s.
pH	7.45	0.0473	7.45	0.0504	3.58	<0.001	n.s.
PaO_2 (mmHg)	64.1	12.8	66.1	15.7	-5.47	<0.001	<0.001
$PaCO_2$ (mmHg)	35.7	6.45	36.1	6.88	-2.26	0.0308	n.s.
O_2 saturation (%)	92.7	5.02	93.2	3.98	-3.9	0.00278	n.s.
CRP (mg/L)	151	120	127	115	8.15	<0.001	<0.001
Urea (mg/dL)	6.94	5.06	7.61	5.51	-5.07	<0.001	<0.001
Glucose (mg/dL)	7.68	3.03	7.64	3.29	0.481	n.s.	n.s.
Sodium (mmol/L)	136	4.48	136	5.1	-2.65	0.00133	0.0862
Age	62.6	18	66.7	17.1	-9.22	<0.001	<0.001
CRB65	0.964	0.8	1.14	0.883	-8.2	<0.001	<0.001
CURB	0.807	0.783	0.931	0.895	-5.94	<0.001	<0.001
CURB65	1.35	1.02	1.56	1.13	-7.97	<0.001	<0.001
CRB	0.423	0.594	0.506	0.678	-5.23	<0.001	<0.001
qSOFA	0.606	0.631	0.679	0.727	-4.28	0.00593	n.s.
Binary variables							
Cough	0.904		0.868		4.53	<0.001	0.000609
Purulent sputum	0.554		0.499		-4.51	<0.001	0.000504
Positive focal auscultation sign	0.803		0.775		2.71	0.00747	n.s.
Male gender	0.613		0.594		-1.51	n.s.	n.s.
Nursing home resident	0.0385		0.125		-13.2	<0.001	<0.001
Smoker	0.322		0.251		6.21	<0.001	<0.001
Former malignancy	0.099		0.12		2.65	0.00925	n.s.
Chronic respiratory disease	0.369		0.39		1.73	n.s.	n.s.
Heart insuffiency	0.187		0.271		8.1	<0.001	<0.001
Other chronic cardiac disease	0.388		0.40		1.03	n.s.	n.s.
Chronic liver disease	0.034		0.038		0.822	n.s.	n.s.
Chronic kidney disease	0.117		0.132		1.8	n.s.	n.s.
Cerebrovascular disease	0.076		0.177		12.5	<0.001	<0.001

Other chronic neurological disease	0.115		0.112		8.49	<0.001	<0.001
Diabetes mellitus	0.208		0.217		0.865	n.s.	n.s.
Other chronic disease	0.112		0.145		-3.9	<0.001	0.00832
Enteral nutrition	0.030		0.047		3.67	<0.001	0.025
Lung operation	0.026		0.035		2.02	n.s.	n.s.
Long term O_2 therapy	0.057		0.072		2.39	0.0191	n.s.
Ventilation	0.012		0.014		0.857	n.s.	n.s.
Vaccination against influenza within the last 12 months	0.38		0.438		4.75	<0.001	<0.001
Vaccination against S. pneumonia within the last 5 years	0.161		0.218		5.87	<0.001	<0.001
Multilobular infiltrate	0.144		0.130		-1.95	n.s.	n.s.
Pleural effusion	0.209		0.198		-1.14	n.s.	n.s.
Dyspnoe	0.738		0.761		2.12	0.0336	n.s.
Pleuralgia	0.409		0.347		5.08	<0.001	<0.001
Confusion	0.172		0.157		11	<0.001	<0.001
Beta blocking agent	0.129		0.14		-1.3	n.s.	n.s.
Preceding antibiotics therapy within the last 4 weeks	0.207		0.19		1.76	n.s.	n.s.
Urine test	0.863		0.796		7.21	<0.001	<0.001
Pneumococcus antigen in urine negative	0.739		0.677		5.42	<0.001	<0.001
Legionella antigen in urine negative	0.8		0.735		6.2	<0.001	<0.001
Respiratory secretion drawn before the first or min 36h after the latest antibiotics treatment	0.226		0.196		2.92	0.0036	n.s.
Respiratory secretion from sputum	0.522		0.415		-8.53	<0.001	<0.001
Leukocytes in respiratory secretion (medium/high)	0.299		0.226		6.53	<0.001	<0.001
Epithelial cells in respiratory secretion (low or medium)	0.34		0.241		8.73	<0.001	<0.001
Tracheobronchial secretion	0.05		0.094		7.1	<0.001	<0.001
EDTA blood	0.783		0.844		5.74	<0.001	<0.001
Differential hemogram	0.288		0.414		-10.6	<0.001	<0.001
Fever	0.332		0.327		0.473	n.s.	n.s.
CRB65>1.75	0.214		0.295		-7.46	<0.001	<0.001

[1] All binary variables are displayed as a fraction of one (1 = 100%)

Table S2. Patient variables of M treated and nM treated patients of the balanced cohort

	Mean M-treated	Standard deviation M-treated	Mean nM-treated	Standard deviation nM-treated	z-Difference	P-value	P-value (corrected)
Scale variables							
BMI	26.1	5.67	26.2	5.7	-0.301	n.s.	n.s.
Systolic blood pressure (mmHg)	131	22.4	131	22.3	-0.465	n.s.	n.s.
Diastolic blood pressure, (mmHg)	74.3	13.1	74.7	13	-0.957	n.s.	n.s.
Heart frequency (/min)	92.8	18.9	92.1	18.6	1.4	n.s.	n.s.
Breath rate (/min)	21.3	5.62	21.3	5.78	0.183	n.s.	n.s.
Temperature (^{0}C)	37.9	1.13	37.9	1.13	0.164	n.s.	n.s.
Leukocytes (/nL)	13.3	5.9	13.2	5.91	0.487	n.s.	n.s.
Hemoglobin (mmol/L)	8.17	1.16	8.17	1.16	0.0728	n.s.	n.s.
Haematokrit (%)	38.8	5.11	38.9	4.99	-0.686	n.s.	n.s.
Thrombocytes (/nL)	254	110	255	109	-0.381	n.s.	n.s.
Average liter O2 suppl. in ventilation during arterial blood gas analysis	0.59	1.45	0.575	1.46	0.351	n.s.	n.s.
pH	7.45	0.0466	7.45	0.0475	0.0607	n.s.	n.s.
PaO_2 (mmHg)	64.6	13.1	65.1	13.2	-1.33	n.s.	n.s.
$PaCO_2$ (mmHg)	35.8	6.5	35.8	6.59	-0.225	n.s.	n.s.
O_2 saturation (%)	92.8	4.93	93	4.26	-1.64	n.s.	n.s.
CRP (mg/L)	146	120	138	117	2.32	0.0229	n.s.
Urea (mg/dL)	7.02	5.15	6.99	4.98	0.209	n.s.	n.s.
Glucose (mg/dL)	7.68	3.1	7.62	2.99	0.637	n.s.	n.s.
Sodium (mmol/L)	136	4.57	136	4.41	-1.2	n.s.	n.s.
Age	63.2	17.7	63.9	17.5	-1.4	n.s.	n.s.
CRB65	0.97	0.805	0.971	0.803	-0.00889	n.s.	n.s.
CURB	0.808	0.79	0.793	0.782	0.673	n.s.	n.s.
CURB65	1.36	1.03	1.36	1.02	0.0836	n.s.	n.s.
CRB	0.42	0.595	0.408	0.592	0.735	n.s.	n.s.
qSOFA	0.599	0.638	0.588	0.641	0.614	n.s.	n.s.
Binary variables							n.s.
Cough	0.898		0.894		0.533	n.s.	n.s.
Purulent sputum	0.545		0.528		-1.37	n.s.	n.s.
Positive focal auscultation sign	0.798		0.797		0.121	n.s.	n.s.
Male gender	0.606		0.615		0.765	n.s.	n.s.
Nursing home resident	0.0437		0.0453		-0.315	n.s.	n.s.
Smoker	0.309		0.293		1.38	n.s.	n.s.
Former malignancy	0.10		0.11		1.33	n.s.	n.s.
Chronic respiratory disease	0.372		0.372		-0.0671	n.s.	n.s.
Heart insuffiency	0.198		0.215		1.73	n.s.	n.s.

Other chronic cardiac disease	0.389		0.385		-0.366	n.s.	n.s.
Chronic liver disease	0.034		0.031		-0.546	n.s.	n.s.
Chronic kidney disease	0.116		0.112		-0.46	n.s.	n.s.
Cerebrovascular disease	0.083		0.079		-0.534	n.s.	n.s.
Other chronic neurological disease	0.061		0.060		-0.136	n.s.	n.s.
Diabetes mellitus	0.209		0.204		-0.481	n.s.	n.s.
Other chronic disease	0.122		0.135		-1.56	n.s.	n.s.
Enteral nutrition	0.030		0.026		-1.08	n.s.	n.s.
Lung operation	0.027		0.027		0	n.s.	n.s.
Long term O_2 therapy	0.062		0.060		-0.407	n.s.	n.s.
Ventilation	0.011		0.010		-0.469	n.s.	n.s.
Vaccination against influenza within the last 12 months	0.381		0.383		0.234	n.s.	n.s.
Vaccination against S. pneumonia within the last 5 years	0.159		0.158		-0.178	n.s.	n.s.
Multilobular infiltrate	0.145		0.149		-0.413	n.s.	n.s.
Pleural effusion	0.207		0.202		-0.523	n.s.	n.s.
Dyspnoe	0.740		0.737		-0.332	n.s.	n.s.
Pleuralgia	0.405		0.4		0.364	n.s.	n.s.
Confusion	0.078		0.077		-0.182	n.s.	n.s.
Beta blocking agent	0.137		0.147		-1.21	n.s.	n.s.
Preceding antibiotics therapy within the last 4 weeks	0.206		0.203		0.282	n.s.	n.s.
Urine test	0.852		0.854		-0.229	n.s.	n.s.
Pneumococcus antigen in urine negative	0.728		0.737		-0.733	n.s.	n.s.
Legionella antigen in urine negative	0.789		0.795		-0.56	n.s.	n.s.
Respiratory secretion drawn before the first or min 36h after the latest antibiotics treatment	0.218		0.214		0.315	n.s.	n.s.
Respiratory secretion from sputum	0.498		0.478		-1.59	n.s.	n.s.
Leukocytes in respiratory secretion (medium/high)	0.282		0.277		0.47	n.s.	n.s.
Epithelial cells in respiratory secretion (low or medium)	0.319		0.302		1.47	n.s.	n.s.
Tracheobronchial secretion	0.056		0.053		-0.357	n.s.	n.s.
EDTA blood	0.805		0.833		2.85	0.0129	n.s.
Differential haemogram	0.316		0.356		-3.34	0.00368	n.s.
Fever	0.325		0.324		0.0347	n.s.	n.s.
CRB65>1.75	0.218		0.222		-431	n.s	n.s

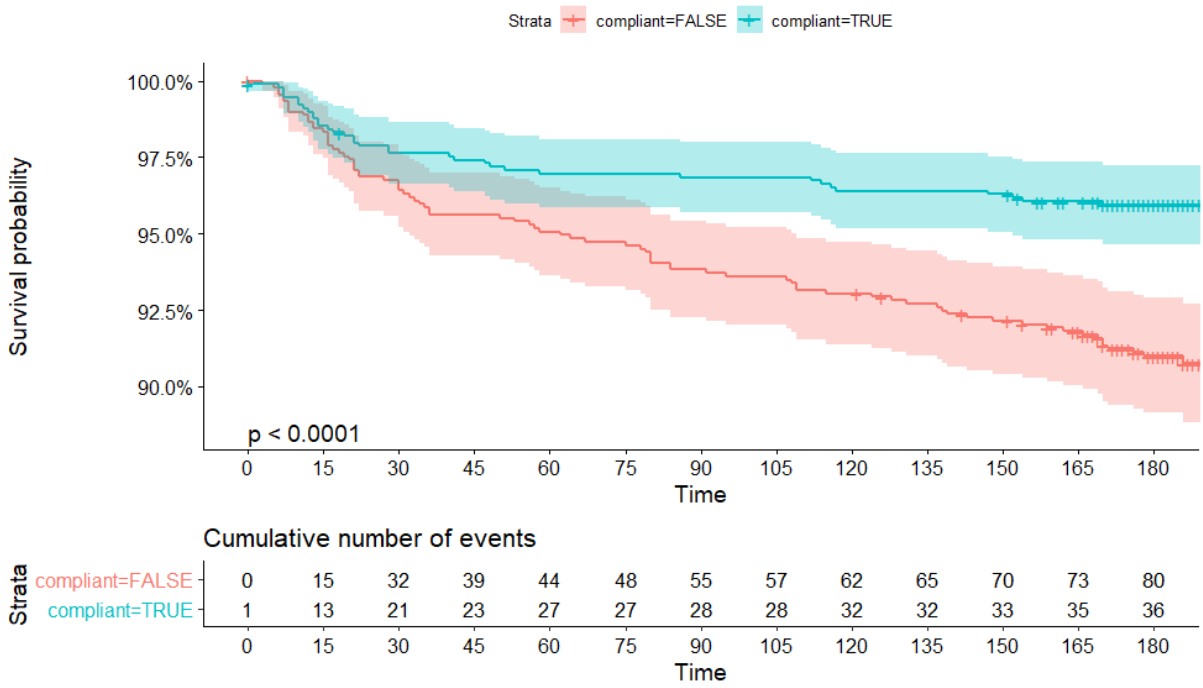


Figure S4. The Kaplan Meier plot when applying our rule.

Table S3. Odds ratios of mono-therapy and different macrolides, when applying our rule and when applying the rule to always apply macrolides

a) With our rule

	Number of M-treated patients	OR	Confidence interval	P-value	Compliant[1], death rate	Non-compliant[2], death rate	Compliance rate[3]
All macrolides, combined[4] therapy	913	2.34	1.56, 3.51	<0.001	0.0394	0.0876	0.708
All macrolides, mono-therapy	50	4.20	0.421, 41.9	n.s.	0.0175	0.0698	0.570
All macrolides, mono- and combined therapy	933[5]	2.36	1.59, 3.52	<0.001	0.0397	0.0890	0.689
Clarithromycin, combined	613	2.36	1.46, 3.84	<0.001	0.0408	0.0914	0.736
Erythromycin, combined	7	1	0.050, 20	n.s.	0.143	0.143	0.714
Roxithromycin, combined	246	1.98	0.899, 4.34	n.s.	0.0407	0.0772	0.602
Azithromycin, combined	44	5.49	0.615, 49	n.s.	0.0217	0.109	0.886
Original death and treatment rate for the combined treated patients and nM-treated controls	913	1	-	-	0.0635	-	0.5

[1] In compliance with the rule

[2] Not in compliance with the rule

[3] Compliance rate is the ratio of patients treated in compliance to our rule

[4] Combined: patients were treated with these macrolides together with a non-macrolide antibiotics

[5] Due to propensity matching, the number patients here is not the sum of the upper two numbers of patients

b) With the rule to always apply macrolides

	Number of M-treated patients	OR	Lower bound	Upper bound	P-value	Compliant, death rate	Non-compliant, death rate

All macrolides, combined therapy	913	1.34	0.920	1.97	n.s.	0.0548	0.0723
All macrolides, mono therapy	50	3.13	0.314	31.1	n.s.	0.020	0.060
All macrolides, mono- and combined therapy	933	1.33	0.917	1.93	n.s.	0.0557	0.0729
Clarithromycin, combined	613	1.67	1.05	2.65	0.029	0.0506	0.0816
Erythromycin, combined	7	1	0.0501	20	n.s.	0.143	0.143
Roxithromycin, combined	246	0.691	0.323	1.48	n.s.	0.0691	0.0488
Azithromycin, combined	44	3.15	0.314	31.5	n.s.	0.0227	0.0682