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Novel approach towards antimicrobial chemotherapy optimization in lower respiratory tract infections in children
An observational study

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Abstract

The use of local antibiogram in guiding clinical decisions is an integral part of the antimicrobial stewardship program. Conventional antibiograms are not disease-specific, ignore the distribution of microorganisms, obscure the in-vitro efficacy interrelationships, and have limited use in polymicrobial infections.

We aimed to develop an in-house empiric, disease-specific, antimicrobial prescription auxiliary for the treatment of hospitalized pediatric pneumonia patients and to present the methods which help to choose the first and the second line antimicrobial therapy, while accounting for cost and safety aspects.

A retrospective single center observational study was conducted on bronchoscopy obtained sputum culture. Analysis of probabilities, variance minimization, Boolean network modeling, and dominance analysis were applied to analyze antibiogram data. The Kirby–Bauer disk diffusion method was used to test the susceptibility of all isolates. Final optimization analysis included local drug acquisition cost (standardized to price per DDD) and safety profile.

Data of 145 pediatric patients hospitalized with pneumonia with 218 isolates over 5 years was collected. A combination of statistical methods such as probabilities of drug efficacy, variance minimization, Boolean network modeling, and dominance analysis can help to choose the optimal first-line and the second-line antimicrobial treatment and optimize patient care. This research reveals that ampicillin is the optimal choice as the first-line drug and piperacillin-tazobactam is the second-line antimicrobial drug if the first one is not effective, while accounting for cost and safety aspects.

The paper proposes a new methodology to adapt empiric antimicrobial therapy recommendations based on real world data and accout for costs and risk of adverse events.

Abbreviations: A = ampicillin, AB = antimicrobial drug, ANOVA = analysis of variance, ASP = antibiotic stewardship program (s), B = Bernoulli distribution, BNA = Boolean network analysis, CAP = community-acquired pneumonia, D = drug, E = expected value, EBIC = extended Bayesian information criterion, HPP = of hospitalized pediatric pneumonia, KPC-Kp = *Klebsiella pneumoniae* carbapenemase producing *Klebsiella pneumoniae*, LSMU = Lithuanian University of Health Sciences, MIC = minimum inhibitory concentration, MPT = modern portfolio theory, R = return, R^2 = the proportion of the variance for a dependent variable, explained by an independent variable in a regression model, SD = standard deviation, spp. = species, var = variance.

Keywords: antibiotic therapy, optimization, pediatric pneumonia

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1. Introduction

Antimicrobial stewardship programs are advocated as a way to combat antimicrobial resistance and this practice has seemingly gained momentum.[1] The antibiotic stewardship programs (ASP) should include the development of facility-specific clinical practice guidelines and pathways for common infections based on local epidemiology, susceptibility patterns, and drug availability or preference.[2] The traditional antibiogram summary (represented with the microorganism incidence and susceptibility description) is a standard component of these programs[3] with well-known shortcomings: the absence of syndrome or disease-specific advice, ignorance of distribution of causative organisms, and is of limited use in the polymicrobial infections.[4,5] The development of clinical decision support systems as a part of the ASP is also cumbersome as such attempts have been made, but quite often resulted in low use and low adherence rate.[6] Despite this, it is recommended to have ASPs and base decisions on local and even disease-specific microbiological data.[7]

Less than judicious use of antimicrobial drugs has led to the development and spread of extensively resistant bacteria, for example, the KPC-producing *Klebsiella pneumoniae*. Because elimination of KPC-producing *K pneumoniae* (KPC-Kp) has failed in most centers where it has become endemic, ASPs have been proposed as means to combat this with limited success.[8–10] One of the strategies to combat the spread of multidrug resistant strains is limiting the use of broad spectrum antimicrobial drugs (e.g., carbapenems) in empiric antibiotic therapy recommendation that can be developed by using the methods currently employed in systems biology.[11]

The antimicrobial susceptibility is quite often presented as a resistance percentage[12,13] and little attention is paid to assess the correlation between the spectra of antimicrobial drugs, that is to account for co-resistance (e.g., between ciprofloxacin, sulphonamides, and gentamicin),[14] or cross-resistance,[15] even though this could be used to help optimize the choice of empiric antibiotic therapy. Several attempts to elucidate the intricate co-occurrence of resistance among bacterial isolates have previously been made. It was established, that Vancomycin minimum inhibitory concentration (MIC) value for methicillin-resistant *Staphylococcus aureus* is correlated with that of teicoplanin and daptomycin MICs.[16] Also, correlation coefficients between antimicrobial susceptibility profiles of over 1600 clinical *S aureus* isolates have been estimated.[17] A dual cross-table antibiogram was also proposed as a method to account for cross-resistance between antimicrobials.[15] The causal probabilistic network was developed to predict the susceptibility to antibiotic therapy while accounting for cross-resistance and treatment history.[18] The Bayesian network analysis was also implemented to aid antimicrobial stewardship programs; one of the strong points of this approach being the statistical rigor and network visualization capability.[19] Another aspect, that should also be brought to attention, is the need to develop a syndrome specific clinical decision support tool for the selection of antimicrobial therapy as described previously.[5] Our work is novel because we repurposed and adapted a framework to identify optimal antimicrobial prescription in terms of in-vitro susceptibility patterns of microorganisms, the covariance between them, while accounting for the most expected adverse drug events and drug acquisition costs. To the best of our knowledge, such an approach has not been used before.

We aimed to develop an in-house empiric, disease-specific, antimicrobial prescription auxiliary for the treatment of hospitalized pediatric pneumonia (HPP) patients and to present the methods which help to choose the first and the second line antimicrobial therapy.

The HPP population was chosen, as there is no consensus whether broad (ceftriaxone, cefuroxime, and cefazolin) or narrow (penicillin, ampicillin, and amoxicillin) antimicrobial therapy is to be prescribed for children hospitalized with pneumonia.[20–22]

The proposed methods are provided with R code and an example dataset, along with proposals regarding the sensitivity analysis and clinical extrapolation of the in vitro data in the Supplementary material, http://links.lww.com/MD/G238.

2. Material and methods

The data set of bacterial sputum culture results was taken from the prospectively maintained database of LSMU microbiology laboratory from December 2014 till December 2019. Patients included in the analysis had acute nonresponsive community-acquired pneumonia or recurrent community acquired pneumonia, defined as persistent fever (38.5 °C) and continuously elevated inflammatory markers in the peripheral blood, clinical condition worsening and consolidation visible on chest radiographs after at least 48 hours of antibiotic treatment. The patients with severe chronic conditions were excluded from this study (e.g., with cystic fibrosis, primary neuromuscular diseases, asplenia, and tuberculosis).[23] The sputum was obtained by bronchoscopy and bronchial lavage[23] from pediatric patients (below 18 years of age). The Kirby–Bauer disk diffusion method on Mueller–Hinton agar was used to test the susceptibility of all isolates. This was a single center retrospective observational study. Data analysis was performed with SAS University Edition and R version 3.5.0.

2.1. Ethical statement

The study was conducted in line with the principles defined in the good clinical practice recommendations[24] and the Declaration of Helsinki.[25] The permission to perform this study was obtained from the Kaunas Regional Biomedical Research Ethics Committee (No. BE-2–17, 2019.12.02). The informed consents were obtained from all parents and/or legal guardians, as the study included only pediatric subjects (<18 years of age).

- The following techniques are used to build the framework to choose antimicrobial drug:
- Probabilities of efficiency. It is the simplest way to choose the most likely efficient drug. However, this method is sensitive to sample data.
- Variance minimization can be useful to choose optimal (the most effective) drug for the first prescription or to establish optimal antimicrobial set.
- Boolean network analysis can be useful to choose optimal (the most effective) drug for the first prescription as well as the most appropriate drug for the second prescription if the first one is not effective.
- Dominance analysis can be useful to choose the optimal drug for the second prescription if the first one is not effective. This method can be used regardless of what drug was prescribed firstly.

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2.2. Probabilistic drug selection

The susceptibility of a random microorganism to a specific drug (D_i) can be treated as Bernoulli trial with 2 possible outcomes, that is, 1 for "success" (i.e., microorganism is susceptible to a drug) and 0 for "failure" (i.e., the microorganism is not susceptible to a drug). In this context, the best estimate of probable drug clinical efficacy is the observed in vitro susceptibility profile of a specific antibiotic drug. The expectation and variance of a Bernoulli distribution[26,27] are:

$E(D_i) = p$, $\mathrm{var}(D_i) = p(1-p)$, where $P(D_i=1) = p$, $P(D_i=0) = 1-p$.

If n independent Bernoulli trials are performed, the random variable D_i for the number of "successes" has a binomial distribution, which is denoted $B(n,p)$. The expectation and variance of a $B(n,p)$ distribution are:

$E(D_i) = np$, $\mathrm{var}(D_i) = np(1-p)$.

Assume that the observed spectrums of in vitro efficacy of drugs are $D_1 \ldots, D_n$. Then $P(D_n)$ is the probability of efficacy and $P(1-P(D_n)) = P(I_n) = i_n$ is the probability of inefficacy. Joint inefficacy probability in the case of events I_1 and I_2 is $P(I_1, I_2) = i_1 i_2$ and conditional inefficacy probability is $P(I_2|I_1) = i_1 i_2 + p\sqrt{i_1(1-i_1) + i_2(1-i_2)}$, where ρ is a Spearman correlation coefficient between the events I_1 and I_2. When $\rho = 0$, $P(I_2|I_1) = P(I_1, I_2)$. In this approach, the consistency constraint is also necessary. When the correlation becomes positive the joint inefficacy probability increases with the correlation. However, if the correlation is negative, then there is no such risk and conditional inefficacy probability is undefined. A similar attempt has been implemented with the Bayesian approach[28] (see Supplementary material, http://links.lww.com/MD/G238).

2.3. Variance minimization

The problem of minimizing the risk of treatment failure is connected to the Markowitz mean-variance portfolio theory, used for solving risk minimization in the stock portfolio construction.[29] The mean-variance analysis is a mathematical framework for assembling a portfolio of assets, such that the expected return is maximized, for a given level of risk. The goal of the mean-variance analysis is to choose the optimal portfolio weighting factors.[29] In this context, an optimal set of weights is the one in which the portfolio achieves an acceptable baseline expected rate of return with minimal volatility.[29] The mean-variance analysis is formulated as follows: assume that there are N risky assets and their rates of returns are given by the random variables $R_1, \ldots, R_N$. Let $w = (w_1, \ldots, w_n)^T$, where w_n denotes the proportion of wealth invested in an asset n, with $\sum_{n=1}^{N} w_n = 1$. The rate of return of such a portfolio is:

$$R_p = \sum_{n=1}^{N} w_n R_n$$

The objective is to evaluate w_n using the mean-variance pair of the portfolio with preferences for higher expected returns $E[R_p]$ and lower variance $\mathrm{var}[R_p]$.[30]

In the context of antimicrobial chemotherapy decision making, the objective is to find the drug which has the highest expected value and the lowest risk of inefficacy. Here R_n is individual observation of specific microorganism's susceptibility to a specific drug, with the corresponding variance. The highest weight in the portfolio has the lowest risk of inefficacy. This was implemented with quadprog package V 1.5–5, built in R to solve Quadratic Programming Problems.[31] An example of the antimicrobial set construction (represented with matrix algebra) is provided in the Supplementary material, http://links.lww.com/MD/G238.

2.4. Modification of the variance minimization algorithm including costs and safety aspects

It was proposed that the observed value of R_i (the expected susceptibility to an antimicrobial drug by a microorganism) can have the following multi-factorial expansion $R_i = \alpha_i + \beta_{i1} F_1 + \ldots + \beta_{iK} F_K + \varepsilon_i$, where α_i and β_{iK} are constants, F_K is a k-th random factor and ε_i is a random disturbance with mean zero and which is uncorrelated with F_K ($k = 1, \ldots, K$) and ε_j ($j \neq i$).[32] This equation can be slightly modified for this specific case: $R_i = \alpha_i \times \ln(C_i \times RRS_i) + \varepsilon_i$, where α_i is an observation of some susceptibility value to an antimicrobial drug (encoded as 1 or 0 for "susceptible" or "resistant", respectively), C_i is cost (e.g., in some relative terms, see Table 1) and RRS is relative risk in safety terms. The safety comparison between beta-lactams and levofloxacin were taken from previous research.[33] It was shown that musculoskeletal disorder incidence (e.g., arthralgia) in levofloxacin treated children was 2.1%, compared with 0.9% in non-fluoroquinolone treated children, with a relative risk estimate of 2.3.[33] *Clostridioides difficile* infection (CDI) risk was also included and was estimated as follows: clindamycin odds ratio (OR) is 16.80, fluoroquino-

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Table 1

Drug acquisition costs.

Drug	ATC	DDD in mg	ROA	One dose in mg	Number of doses per package	Price per package + VAT (Eur)	Price per mg	DDD price
Meropenem	J01DH02	3000	P	1000	10	107.2	0.011	32.16
Ampicillin	J01CA01	6000	P	1000	50	33.83	0.001	4.06
Ampicillin-sulbactam	J01CR04	1500	O	375	12	8.04	0.002	2.68
Cefotaxime	J01DD01	4000	P	1000	10	20.59	0.002	8.24
Cefuroxime	J01DC02	3000	P	1500	10	25.8	0.002	5.16
Levofloxacin	J01MA12	500	O	500	7	9.59	0.003	1.37
Piperacillin-tazobactam	J01CR05	14000	P	4500	10	56.61	0.001	17.61
Amoxicillin-clavulanate	J01CR02	3000	P	1200	5	17.82	0.003	8.91

ATC = the anatomical therapeutic chemical classification, DDD = the defined daily dose, mg = milligram, O = oral, P = parenteral, ROA = route of administration, VAT = value added tax, prices were obtained from http://kainynas.vlk.lt/idrug-public-app/search/mode/uncompensated.0.

lones OR is 5.50, and cephalosporins, monobactams, and carbapenems OR is 5.68, macrolides OR is 2.65, sulfonamides and trimethoprim OR is 1.81, and penicillins OR is 2.71. In the same publication, tetracyclines had a negligible risk of CDI OR 0.92.[34] We did not find studies comparing the risk of resistance development across different antimicrobial drug groups and resistance development was previously described to all antimicrobial drug classes, thus the equal risk of resistance across different antimicrobial drug groups was assumed.[35]

2.5. Boolean network analysis

A network is a system of variables (called nodes), that are interconnected at the edges [connections] and represent conditional dependencies. An edge between the variables X_1 and X_2 indicates a non-spurious relationship, that cannot be explained by any other variables. Conversely, if the variables X_1 and X_2 are not connected, the inverse is true (despite the observed correlation, that disappears upon conditioning on all other variables).[36] The Boolean networks are logical models, described by asynchronous state transition graphs, that represent all the possible exits from every single state, giving a global image of all the possible trajectories of the system. They may be used to represent complex biological systems.[37] The networks can be used to present the causal structure of data or the correlation structure of the data.[38]

The networks were estimated with the eLasso procedure, as implemented in the R package IsingFit (http://cran.r-project.org/web/packages/ IsingFit/IsingFit.pdf). The eLasso is a computationally efficient method, based on Ising models, to estimate the weighted, undirected networks from binary data, that merge the logistic regression and model selection (based on a goodness-of-fit measure), to identify the relevant relationships between variables and assess the network structure.[36] The eLasso procedure regresses each variable on all other variables in turn. The best-fitting regression function is selected based on the minimization of extended Bayesian information criterion (EBIC).[39] The independent variables included in the selected regression function indicate the nodes, that the dependent variable is connected to by edges, which are weighted by the parameters of regression.[38] The model can be made parsimonious with a hyperparameter (or gamma value), that imposes a penalty on the regression coefficients and plays a role in the goodness-of-fit measure EBIC with which the optimal tuning parameter (which represents the best set of neighbors of the focal node) is selected.[36] In essence, the gamma penalizes the number of nodes in the neighborhood selection and puts an extra penalty on the number of neighbors. If gamma increases, the strength of the extra penalty on the size of the model space also increases (and the opposite is true). The higher value of gamma reduces the number of false positives and increases power (improves the ratio of a number of nodes and observations).[36] Misspecification of the penalty parameter may result in the misrepresentation of the true underlying network.[36]

The graph in the BNA is represented as an adjacency matrix. We write 1 at the ith row and jth column of the matrix if there is an edge between ith and jth nodes. 0 indicates no edge between nodes.[40] This matrix is symmetric and has all zeroes in the diagonal.[41] In our context, the nodes represent the different drugs, while edges represent the relationship between the drug antimicrobial spectra.

2.6. Dominance analysis

The dominance analysis shows if one independent variable contributes more unique variance than other independent variables, either across all possible multiple linear regression sub-models or on average across models of all possible subset sizes. This analysis involves computing each predictor's incremental validity across all possible sub-models. If the incremental validity is always higher for X_i than for X_j for every sub-model, then X_i is said to have complete dominance over X_j. The conditional dominance is a relaxed version of dominance and occurs when the average incremental variance within each sub-model of sizes 0 to $p - 1$ (p is number of predictors) is greater for one predictor than another across all model sizes.[42] The conditional dominance weights are average incremental variance components, used to evaluate the conditional dominance and partition the model R^2 across predictors. The dominance weights aid in the assessment of a predictor contribution to a criterion, sum up to the overall model R^2 and elucidate the properties of model predictors.[42]

The complete, conditional, and general dominance values (D_{ij}) for each pair of predictors are usually presented in the paired dominance metrics table. A value of 1 in D_{ij} indicates that X_i dominates X_j, 0 indicates that X_j dominates X_i, and 0.5 indicates that dominance cannot be established between X_i and X_j.[42]

In our case, when choosing the second line empiric antimicrobial therapy we seek to prescribe an antimicrobial that has a different antimicrobial spectrum from the previously prescribed antimicrobial drug. Thus, we need to find the worst predictor with the smallest contribution to overall model R^2.

Table 2		
The frequency of microorganisms.		
Microorganism	**N**	**Percentage**
Staphylococcus aureus	53	25
Haemophilus influenzae	34	16
Streptococcus pneumoniae	34	16
Pseudomonas aeruginosa	19	9
Escherichia coli	11	5.2
Klebsiella pneumoniae	11	5.2
Enterobacter cloacae	4	1.9
Klebsiella oxytoca	9	4.2
Stenotrophomonas maltophilia	4	1.9
Citrobacter freundii	3	1.4
Enterobacter aerogenes	3	1.4
Streptococcus group CFG (small colony)	2	0.9
Streptococcus beta-hemolytic ACG (large colony)	2	0.9
Enterobacter kobei	2	0.9
Enterobacter ludwigii	2	0.9
Streptococcus dysgalactiae	2	0.9
Moraxella (Branhamella) *catarrhalis*	2	0.9
Streptococcus pyogenes (Strep. group A)	2	0.9
Enterobacter asburiae	2	0.9
Providencia rettgeri	2	0.9
Serratia marcescens	2	0.9
Streptococcus agalactiae (Strep. group B)	1	0.5
Streptococcus group C (small colony)	1	0.5
Enterobacter hormaechei	1	0.5
Streptococcus group F	1	0.5
Acinetobacter species	1	0.5
Proteus mirabilis	1	0.5
Burkholderia dolosa	1	0.5

3. Results

We analyzed the bronchial secrete data of 145 pediatric patients hospitalized with lower respiratory tract infections. Two hundred eighteen isolates were identified (Table 2).

3.1. Probabilistic drug selection

The expected value of microorganisms' susceptibility to a drug was calculated as a mean (or probability). All isolates were susceptible to levofloxacin, 97%—to meropenem, 93%—to piperacillin-iazobactam, 91%—to cefotaxime, 76%—to ampicillin-sulbactam and 60%—to ampicillin. Ampicillin was considered as a first-choice drug, because levofloxacin, meropenem, piperacillin-tazobactam, and cefotaxime should be avoided as first-line drugs, due to an overly broad spectrum (that is high "collateral damage") or safety issues.[43–45] The probabilistic approach allows for various drug selection scenarios, presented under 3 strategies (optimal, bold, and suboptimal) based on probabilities as presented in Table 3, this approach is presented to better elucidate, the concept of our approach, however, variance minimization is proposed as a generalization.

3.2. Minimum variance antimicrobial set

A minimum variance set was constructed using the susceptibility data (the variance–covariance matrix is presented in Table 4) and helps to find an optimal antimicrobial set in terms of efficacy probability and covariance. The penicillin, clindamycin, erythro-

mycin, gentamicin, oxacillin, and vancomycin were effective only in 11%, 12%, 8%, 35%, 17%, and 45% of cases, respectively; thus were omitted as viable empiric antimicrobial therapy options. Trimethoprim and sulfamethoxazole combination does not have a licensed therapeutics indication for the treatment of pneumonia, thus it was also excluded from the analysis.[46]

The weights of minimum variance antimicrobial portfolio were calculated for several portfolios as shown in Table 5. These results indicate that in this population empiric antimicrobial therapy should consist of ampicillin and some broad-spectrum antimicrobial drug (levofloxacin, meropenem, or piperacillin-tazobactam). We conducted an additional variance minimization analysis and included costs (Table 1) and safety aspects where it seems, that ampicillin is a very reasonable first-line drug with piperacillin and tazobactam as the second-line drug (Table 6, Run 4). It may also be very reasonable in terms of costs (Table 6) and safety aspects to initiate treatment with ampicillin-sulbactam (as is currently done in our pediatrics unit) and the switch to piperacillin-tazobactam if treatment with ampicillin-sulbactam is ineffective.

3.3. Boolean network analysis (BNA)

The weight adjacency matrix of the BNA aids the second-line drug selection. The estimated network in the form of a weight adjacency matrix is presented in Table 7, where the estimated thresholds of a variable represent the presence of autonomous disposition. For the network when gamma equals 0, all the

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Table 3

The framework of drug selection under 3 strategies (costs and safety aspects excluded).

	1st line	2nd line	Joint inefficacy P	Conditional inefficacy P
Optimal	Ampicillin (0.40)	Piperacillin-Tazobactam (0.088)	.035	.423
Bold	Ampicillin (0.40)	Levofloxacin (0.005)	.002	.341
Sub-optimal	Ampicillin (0.40)	Ampicillin-sulbactam (0.24)	.095	.541

Notes: drug name and probability (P), P represents probabilities of inefficacy p (inefficacy) $= 1 − p$ (efficacy).

Table 4

Variance covariance matrix (costs and safety aspects excluded).

	Ampicillin	Ampicillin-Sulbactam	Cefotaxime	Cefuroxime	Levofloxacin	Meropenem	Piperacillin-Tazobactam	Amoxicillin-Clavulanate
Ampicillin	0.241	0.144	0.083	0.133	0.003	0.025	0.053	0.13
Ampicillin-sulbactam	0.144	0.182	0.108	0.159	0.004	0.032	0.067	0.151
Cefotaxime	0.083	0.108	0.151	0.116	0.004	0.034	0.071	0.103
Cefuroxime	0.133	0.159	0.116	0.172	0.004	0.032	0.068	0.137
Levofloxacin	0.003	0.004	0.004	0.004	0.005	0.004	0.004	0.004
Meropenem	0.025	0.032	0.034	0.032	0.004	0.04	0.029	0.033
Piperacillin-tazobactam	0.053	0.067	0.071	0.068	0.004	0.029	0.08	0.069
Amoxicillin-clavulanate	0.13	0.151	0.103	0.137	0.004	0.033	0.069	0.17

Table 5

Optimization runs (costs and safety aspects excluded).

	Ampicillin	Ampicillin-Sulbactam	Cefotaxime	Cefuroxime	Levofloxacin	Meropenem	Piperacillin-Tazobactam	Amoxicillin-Clavulanate
Run 1	0.01	0	0	0	0.99	0	0	0
Run 2	0.04	0	0	0	X	0.81	0.15	0
Run 3	0.12	0	0.04	0	X	X	0.84	0
Run 4	0.19	0	0.54	0.02	X	X	X	0.25
Run 5	0.17	0	X	0.39	X	X	X	0.44

Table 6

Optimization runs (costs and safety aspects included).

	Ampicillin	Ampicillin-Sulbactam	Cefotaxime	Cefuroxime	Levofloxacin	Meropenem	Piperacillin-Tazobactam	Amoxicillin-Clavulanate
Run 1	0	0.02	0	0	0.98	0	0	0
Run 2	0.04	0.58	0	0	X	0.31	0.07	0
Run 3	0.04	0.73	0	0	X	X	0.23	0
Run 4	0.44	X	0	0	X	X	0.56	0
Run 5	0.6	X	0.22	0	X	X	X	0.17

thresholds are negative. This means that no drug has an autonomous disposition. The levofloxacin has the highest threshold (-inf), thus the highest probability of being present in the sample compared to the other drugs. Different Boolean networks were built by gradually increasing the gamma parameter (see Supplementary material, http://links.lww.com/MD/G238).

Table 7

Network estimation run 5, adjacency matrix: network density: 0.19, gamma=4, rule used: And-rule.

	Ampicillin	Ampicillin-Sulbactam	Cefotaxime
Ampicillin	0.00	4.16	0.00
Ampicillin-sulbactam	4.16	0.00	0.00
Cefotaxime	0.00	0.00	0.00
Cefuroxime	5.38	4.07	3.57
Levofloxacin	0.00	0.00	0.00
Meropenem	0.00	0.00	0.00
Piperacillin-tazobactam	0.00	0.00	2.05
Vancomycin	6.67	0.00	0.00
Amoxicillin-clavulanate	0.00	3.08	0.00
	Cefuroxime	Levofloxacin	Meropenem
Ampicillin	5.38	0.00	0.00
Ampicillin-sulbactam	4.07	0.00	0.00
Cefotaxime	3.57	0.00	0.00
Cefuroxime	0.00	0.00	0.00
Levofloxacin	0.00	0.00	0.00
Meropenem	0.00	0.00	0.00
Piperacillin-tazobactam	0.00	0.00	0.00
Vancomycin	0.00	0.00	0.00
Amoxicillin-clavulanate	0.00	0.00	0.00
	Piperacillin-Tazobactam	Vancomycin	Amoxicillin-Clavulanate
Ampicillin	0.00	6.67	0.00
Ampicillin-sulbactam	0.00	0.00	3.08
Cefotaxime	2.05	0.00	0.00
Cefuroxime	0.00	0.00	0.00
Levofloxacin	0.00	0.00	0.00
Meropenem	0.00	0.00	0.00
Piperacillin-tazobactam	0.00	0.00	0.00
Vancomycin	0.00	0.00	0.00
Amoxicillin-clavulanate	0.00	0.00	0.00
Estimated thresholds:	Ampicillin −17.36	Ampicillin-Sulbactam −4.38	Cefotaxime −1.00
	Cefuroxime −5.72	Levofloxacin -Inf	Meropenem 3.15
	Piperacillin-Tazobactam −0.72	Vancomycin −3.15	Amoxicillin-Clavulanate −0.57

The network constructed with gamma=4 is the sparsest. The results show that the strongest relationship (gamma equals 4) can be established between the ampicillin and ampicillin-sulbactam, ampicillin and vancomycin, ampicillin and cefuroxime (Fig. 1). This means, that in case of treatment failure with ampicillin, switching to ampicillin-sulbactam or cefuroxime or vancomycin (due to low Methicillin-resistant *S aureus* [MRSA] prevalence in our sample) is unlikely to cover a clinically significantly different spectrum of microorganisms, as shown graphically (Fig. 1: [the green edges represent a positive relationship between the drugs]).

3.4. Selection of the second line empiric antibiotic therapy with dominance analysis

The results of the dominance analysis are presented in Table 8. The table of paired dominance metrics contains the complete, conditional, and general dominance values for each pair of predictors. If D_{ij} is 1, it indicates that X_i dominates X_j, 0 indicates
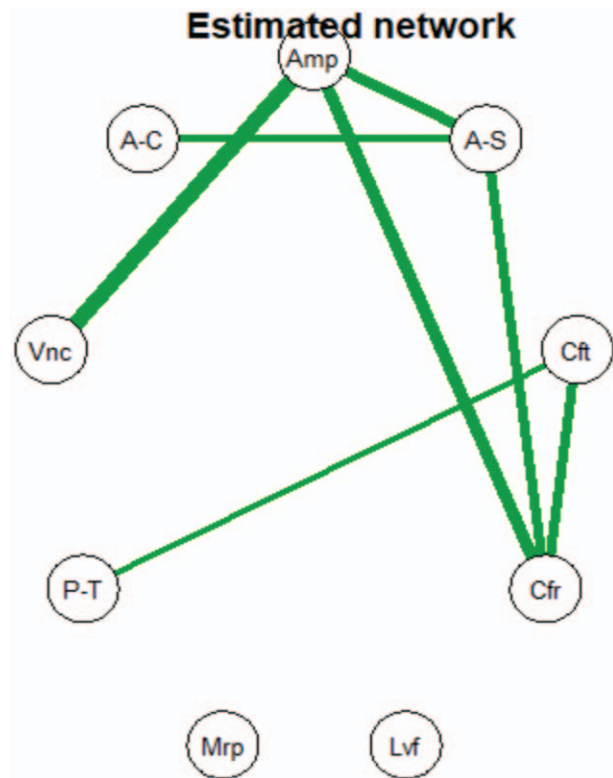

Figure 1. Network estimation run 5. Network density: 0.19, Gamma=4, rule used: And-rule.

Table 8

Paired dominance metrics.

	Complete	Conditional	General
AS>CFT	1	1	1
AS>CFU	1	1	1
AS>LEV	1	1	1
AS>MER	1	1	1
AS>PT	1	1	1
AS>AC	1	1	1
CFT>CFU	0	0	0
CFT>LEV	1	1	1
CFT>MER	1	1	1
CFT>PT	1	1	1
CFT>AC	0	0	0
CFU>LEV	1	1	1
CFU>MER	1	1	1
CFU>PT	1	1	1
CFU>AC	0.5	0.5	1
LEV>MER	0.5	0	0
LEV>PT	0.5	0	0
LEV>AC	0	0	0
MER>PT	0.5	0	0
MER>AC	0	0	0
PT>AC	0	0	0

that X_j dominates X_i, and 0.5 indicates that dominance cannot be established between the X_i and X_j.

Several scenarios were analyzed. In the case of ampicillin as a dependent variable, the D_{ij} values for general dominance (Gen) indicate that ampicillin-sulbactam > amoxicillin-clavulanate > cefuroxime / cefotaxime > piperacillin-tazobactam > meropenem > levofloxacin.

It means that if the ampicillin is prescribed firstly, then ampicillin-sulbactam is the most similar drug. Meanwhile, the levofloxacin is the worst predictor, in this case, thus the most suitable alternative for the second line empiric antimicrobial therapy.

4. Discussion

This research focuses on the potential methodological approaches in choosing empiric antimicrobial therapy, based on real-world data. The minimum variance optimization may be useful when one or a combination of drugs should be chosen for the empiric treatment. The Boolean network analysis seems to provide a comprehensible visual understanding of relationships between the patterns of antimicrobial susceptibility spectra, other methods, namely, the dominance analysis and probability analysis is most appropriate when a scenario analysis is performed.

The literature review reveals that after exclusion of the atypical pathogens (e.g., *Mycoplasma pneumoniae*, with laboratory tests) the treatment of community-acquired pneumonia in children should usually be started with amoxicillin for outpatients, and with ampicillin, Penicillin G for the inpatients. If the child is not fully immunized, he/she can be treated with a third-generation parenteral cephalosporin (e.g., ceftriaxone) or cefuroxime (a second-generation cephalosporin), while gentamicin, ciprofloxacin, and meropenem should be used in specific cases and not as an empiric antibiotic therapy.[47] However, some authors argue that

either broad (ceftriaxone/cefotaxime) or narrow (ampicillin/penicillin) spectrum antimicrobial therapy may be prescribed for children, hospitalized with pneumonia.[20] Interestingly, a fairly recent systematic review concluded, that for the treatment of pediatric outpatients with community-acquired pneumonia (CAP) amoxicillin is an alternative to co-trimoxazole and somewhat preferred over co-amoxyclavulanic acid and Cefpodoxime, due to limited amount of evidence. It was also concluded that for hospitalized pediatric patients with severe and very severe CAP, penicillin/ampicillin plus gentamicin is superior to chloramphenicol and that for such patients coamoxyclavulanic acid and cefuroxime are viable alternatives.[48]

Our research shows, that, accounting for coresistance among bacterial isolates, the levofloxacin seems to cover the majority of observed pathogens, followed by meropenem and piperacillin-tazobactam, drugs usually reserved for complicated infections.[49,50] After the exclusion of these antimicrobials, we show that ampicillin or ampicillin-sulbactam may be the best choice in this population taking into account drug price and safety aspects. Our results seemingly contradict the results of a fairly recent review, advocating the use of penicillin/ampicillin with gentamicin in such population.[48]

The proposal to understand antimicrobial in vitro efficacy as a binary variable is operating under the assumption that intermediate susceptibility (in our dataset one culture of *Stenotrophomonas* had intermediate susceptibility to Ceftazidime) equals resistance.[15] It has clinical merit, as there is some evidence to link intermediate susceptibility to treatment failure.[51] The choice of second-line antimicrobial therapy, covered in this research, is a common problem in the clinical environment, however, there is a pronounced lack of data to support evidence-based measures in this area.[52]

The authors are aware of the new rapid molecular diagnostic technologies for infectious diseases that help to establish accurate microbiological diagnoses, however these methods still take time (at least a few hours), Kirby–Bauer disk diffusion method remains the gold standard technique and there still remains a need to develop the empiric antibmicrobial therapy reccomendations.[53]

4.1. Limitations

The main limitation of this research is that is was conducted in single center and is retrospective in nature. The treatment recommendations, presented in this article, are only valid for the inpatient pediatric pneumonia population, in patients, that are candidates for bronchoscopy (that has a complicated case of paediatric pneumonia requiring hospitalization) and the authors refrain from making generalized conclusions regarding the treatment of the paediatric CAP or nosocomial pneumonia. The main analysis is based on the assumption that the atypical pathogens (e.g., *M pneumonia*, with laboratory tests) were excluded.

5. Conclusions

The paper proposes a new methodology to adapt empiric antimicrobial therapy recomendations based on real data. All the methods presented in the paper can be combined together in order to compare the results and find the optimal first-line as well as the second-line antimicrobial treatment. The treatment recommendations presented in this article are valid for the inpatient pediatric pneumonia population.

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