Optimizing Empiric Antibiotic Therapy: a Probabilistic Approach

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Background

How to start optimal antibiotic therapy before the results of cultures and antimicrobial susceptibility tests are available?

Here, we use the law of total probability to present a probabilistic approach based on antibiograms of bacterial isolates from healthcare and community-acquired infections to optimizing empiric antibiotic therapy.

Methods

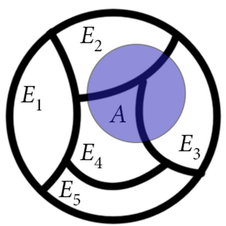
Data on the microbiology of healthcare and community-acquired infections were analyzed from hospitals in Belo Horizonte, a three million inhabitants city from Brazil. Healthcare infections were defined by the National Healthcare Safety Network (NHSN)/CDC protocols. Only data obtained from infections with positive culture, both hospital and community, were considered.

The success rate of an antibiotic (ATB) regimen, considering just one drug individually (monotherapy), was calculated by Law of Total Probability (Fig 1). In this sense, if a microorganism has not been tested for a specific antimicrobial, then, by definition, it was considered an antibiotic failure.

For a regimen with more than one antibiotic, if the microorganism is sensitive to one of them, then it was considered a success of the scheme. For calculating the success probability of two or three antimicrobials A, B, and C, simultaneously (Fig 2), i.e., P(A and B) or P(A and B and C), the sensitivity to an antimicrobial was considered independent of sensitivity to any other. Then, P(A and B) = P(A) * P(B), and P(A and B and C) = P(A)*P(B) *P(C).

Figure 1 - Law of total probability: success rate of an antibiotic considering just one drug individually (monotherapy).

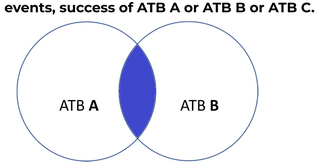
$$P(A) = \sum_{i=1}^{n} P(E_i \cap A) = \sum_{i=1}^{n} P(E_i) \times P(A/E_i)$$



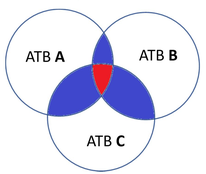
Where:

- E_1, E_2, E_3, ...E_i = i-th etiological agent of the infection
- $P(E_i)$ = chance of infection being caused by the i-th etiologic agent.
- n = total number of different etiologic agents of infection.
- **A** = any antimicrobial "A" being successful in treating the infection.
- **P(A)** = probability of an antimicrobial "A" being successful in treating the infection in a global way, for whatever the etiologic agent of the infection.
- P(A|E_i) = probability of antimicrobial "A" being successful in treating the infection, **knowing which etiologic agent is causing the infection**.

Figure 2 – Probability of the union of two events, success of ATB A or ATB B, and union of three events, success of ATB A or ATB B or ATB C.



$$A \cup B = A + B - A \cap B \Rightarrow P(A \cup B) = P(A) + P(B) - P(A \cap B)$$



$$A \cup B \cup C = A + B + C - A \cap B - A \cap C - B \cap C + A \cap B \cap C$$

$$P(A \cup B \cup C) = P(A) + P(B) + P(C) - P(A \cap B) - P(A \cap C) - P(B \cap C) + P(A \cap B \cap C)$$

Results

Microbiologic data from hospital acquired infections (HAI) and community-acquired infections (CAI) are analyzed once a year.

Empiric antibiotic therapy to HAI were proposed for urinary tract infections (UTI), bloodstream infections (BSI), and pneumonia (Figures 2 and 3). Empiric antibiotic therapy to community-acquired infections were developed for UTI, pneumonia, gastrointestinal system infection, bone and joint infection, and skin and soft tissue infection.

Figure 3 – Success rate of each antibiotic alone, considering just one drug individually (monotherapy): analysis of hospital-acquired pneumonia.

Etiological agent of the Pneumonia	Total number of different etiologic agents of infection	Chance of pneumonia being caused by the i-th etiologic agent	P(A|Ei) = probability of antimicrobial "A" being successful in treating the infection, knowing which etiologic agent is causing the infection.															
			Amikacin		Clavulan		Gentamicin		Linezolid		Norfloxacin		Oxacillin		Ciprofloxacin		SMX-TMP		Meropenem	
			n	S	n	S	n	S	n	S	n	S	n	S	n	S	n	S	n	S
Pseudomonas	14	32%	12	100%	0	0%	8	100%	0	0%	0	0%	0	0%	12	92%	0	0%	13	69%
Klebsiella	7	16%	6	100%	1	100%	7	100%	0	0%	0	0%	0	0%	5	80%	2	100%	6	83%
SARS-CoV-2	5	11%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
Acinetobacter	3	7%	0	0%	0	0%	2	100%	0	0%	0	0%	0	0%	2	50%	0	0%	3	33%
Stenotrophomonas	3	7%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	3	100%	0	0%
Enterobacter	2	5%	1	100%	1	100%	2	100%	0	0%	0	0%	0	0%	2	100%	0	0%	2	100%
Serratia	2	5%	2	100%	0	0%	2	100%	0	0%	0	0%	0	0%	2	100%	0	0%	2	100%
Proteus	2	5%	2	100%	1	100%	2	100%	0	0%	0	0%	0	0%	1	100%	1	0%	2	100%
Candida	2	5%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
Enterococcus	1	2%	0	0%	0	0%	1	100%	1	100%	0	0%	0	0%	0	0%	0	0%	0	0%
Morganella	1	2%	1	100%	0	0%	1	100%	0	0%	0	0%	0	0%	1	100%	1	100%	1	100%
Citrobacter	1	2%	1	100%	0	0%	1	100%	0	0%	0	0%	0	0%	1	100%	0	0%	1	100%
Streptococcus	1	2%	0	0%	0	0%	1	100%	1	100%	0	0%	0	0%	0	0%	1	0%	0	0%
Total	**44**	**100%**	**66%**		**23%**		**77%**		**5%**		**0%**		**0%**		**64%**		**23%**		**56%**	

P(A) = probability of an antimicrobial "A" being successful in treating the infection in a global way, for whatever the etiologic agent of the infection.

Figure 4 – Success rate of one, two or three antibiotics: analysis of hospital-acquired pneumonia.

Antibiotic regimen	Probability of the antimicrobial regimen being successful in treating the pneumonia in a global way, for whatever the etiologic agent of the infection.
Gentamicin + Meropenem + Vancomycin	90%
Gentamicin + Meropenem	90%
Gentamicin + Ceftazidime	89%
Amikacin + Meropenem + Vancomycin	86%
Amikacin + Meropenem	85%
Amikacin + Ceftazidime	83%
Ciprofloxacin + Ceftazidime	82%
Gentamicin	77%
Amikacin	66%
Ciprofloxacin	64%
Vancomycin + Cefepime	58%
Vancomycin + Meropenem	58%
Cefepime	56%
Meropenem	56%
Vancomycin + Ceftazidime	53%
Ceftazidime	51%
Ceftriaxone	41%
SMX-TMP	25%
Amoxicillin clavulan	25%
Ampicillin/sulbactan	18%
Ampicillin	17%
Teicoplanin	5%
Penicilina oral	2%
Rifampicina	2%

Figure 5 - Probability of the antimicrobial regimen being successful in treating an infection according to the length of stay at hospital.

Antibiotic regimen	up to 7 days of hospitalization	from 8 to 14 days of hospitalization	over 14 days of hospitalization
Gentamicin + Meropenem + Polimyxin B	88%	84%	79%
Amikacin + Meropenem + Polimyxin B	84%	66%	76%
Gentamicin + Polimyxin B + Vancomycin	77%	86%	76%
Gentamicin + Meropenem + Vancomycin	91%	88%	75%
Gentamicin + Ciprofloxacin	81%	75%	73%
Amikacin + Polimyxin B + Vancomycin	69%	70%	72%
Amikacin + Meropenem + Vancomycin	88%	75%	71%
Gentamicin + TMP-SMX	86%	82%	71%
Amikacin + Ciprofloxacin	75%	48%	70%
Polimixa B + Meropenem + Vancomycin	73%	72%	68%
Gentamicin + Meropenem	88%	79%	67%
Amikacin + TMP-SMX	81%	63%	67%
Gentamicin + Cefepime	78%	74%	63%
Amikacin + Meropenem	84%	56%	62%
Gentamicin + Ceftazidime	74%	73%	62%
Gentamicin + Vancomycin	77%	81%	62%
Gentamicin + Ceftriaxone	78%	74%	60%
Amikacin + Cefepime	72%	45%	58%
Amikacin + Ceftazidime	65%	45%	57%
Amikacin + Vancomycin	69%	61%	57%
Gentamicin + Oxacillin	74%	72%	54%
Amikacin + Ceftriaxone	71%	46%	54%
Gentamicin	68%	67%	50%
Meropenem + Vancomycin	73%	64%	50%
Cefepime + Oxacillin + Piperacilina/Tazobactan	65%	50%	48%
Amikacin + Oxacillin	66%	41%	48%
Ciprofloxacin	40%	25%	46%
Cefepime + Ampicillin	39%	30%	43%
Amikacin	58%	31%	43%
TMP-SMX	56%	47%	42%
Polimixa B + Oxacillin	20%	35%	41%
Meropenem + Oxacillin	70%	46%	39%
Meropenem	63%	36%	34%
Cefepime	33%	21%	26%
Ceftazidime	18%	20%	24%
Vancomycin	28%	44%	24%
Ampicillin	9%	12%	24%
Piperacilina/Tazobactan	34%	25%	24%
Ceftriaxone	31%	21%	19%
Oxacillin	20%	15%	8%

Conclusions

We presented here a probabilistic approach to empiric antibiotic therapy.

The next step is to validate all proposed regimens, that can be used to improve the success likelihood of empiric antibiotic decision making.

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