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Therapeutic efficacy of different antibiotics against pathogenic non-fermenters for appropriate selection of drugs

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Abstract

Pathogenic non-fermenters are being increasingly isolated from clinical specimens and are usually multidrug resistant, thus limiting the treatment possibilities. The aim of this study was to determine the Efficacy Ratio (ER) of different antibiotics against *Pseudomonas aeruginosa* and *Acinetobacter baumannii-calcoaceticus*(ABC) complex for appropriate drug selection.A total of 122 isolates which consisted of 78 *P.aeruginosa* and 44 ABC complex isolates obtained from blood cultures of patients were included in the study. All isolates were tested for minimum inhibitory concentration (MIC) by VITEK 2. Then the ER was calculated for each isolate using the formula, ER = Susceptible breakpoint MIC ÷ MIC of isolate. The ER < 1 when drugs were resistant and ≥ 1 when susceptible. Higher the ER value, more effective the antibiotic will be.

Introduction

Pathogenic non-fermenting Gram negative bacilli cause serious infections, particularly healthcare-associated and are generally multidrug resistant(1). The most common organisms are *Pseudomonas aeruginosa* and *Acinetobacter baumannii-calcoaceticus* (ABC) complex (1). Both are ubiquitous organisms which are capable of causing severe systemic infections. The rising resistance shown by them have restricted the antimicrobial options available for treatment. Thus, increasing the mortality, duration of admission and cost (1).

The effectiveness of an antibiotic in clinical use depends on the host, the drug and the causative organism (2). The susceptibility of the organism to an agent can be assessed by in-vitro susceptibility testing. A quantitative method of measuring susceptibility is the estimation of minimum inhibitory concentration (MIC) which indicates the concentration of antibiotic required to inhibit the growth of the pathogen(3). It helps in calculating the dose that needs to be customized for administration. Additionally, MIC is useful to the clinician to compare the relative efficacies of the different susceptible agents to choose the most effective agent(4). The effective drug is not chosen by the higher numerical value among the susceptible MIC, rather by how far the MIC of that drug is from its breakpoint MIC. As the breakpoint MIC is different for each drug, the relation between MIC and the breakpoint MIC for a drug is calculated as Efficacy Ratio. Wherein, higher efficacy ratio is expressed astherapeutic efficacy of the drug(2). It is a better indicator of how effective a drug will be against a pathogen.

Material & Methods

A prospective observational study was conducted in the Department of Clinical Microbiology, Christian Medical College, Vellore from April to December 2017. All *P.aeruginosa* and *A.baumannii-calcoaceticus* complex (ABC) isolates from blood culture were identified using standard procedures (5) and included in the study. Minimum inhibitory concentration (MIC) was determined for all the isolates by VITEK 2.

The procedure in brief: an8-24 hour old, pure subculture of each isolate,grown on QC passed 7% sheep blood agar was used for testing. The antimicrobial susceptibility test was done on VITEK 2 Compact as per the manufacturer's instructions (bioMérieux, France). Three ml of sterile saline provided with the kit was taken into two un-sensitized tubes, also provided by the manufacturer. In the first tube, 1-2 colonies of the organism to be tested was inoculated. A suspension was made of turbidity 0.5-0.63 McFarland standards, adjusted using a calibrated VITEK 2 DensiChek instrument. From this suspension, 160 µl was transferred to the second un-sensitized tube con-

taining 3ml of saline and mixed well. Following which, AST card no. N281 was inserted and the inoculum was loaded into the VITEK 2 Compact instrument within 30 minutes of preparation. The results were obtained within 16 hours.

After obtaining the MIC value, Efficacy Ratio (ER) for each antibiotic was calculated using the formula, ER = Susceptible breakpoint MIC/ MIC of isolate(2). The breakpoint MIC value for each antibiotic was taken from Clinical and Laboratory Standards Institute (CLSI) guidelines for2017(6).

Results

The total number included in the study was 122, of which 78 (64%) were *P.aeruginosa* isolates and 44 (36%) were ABC complex isolates. All the resistant strains had an ER< 1 and the susceptible oneshad an ER ≥ 1.ER ≥ 2 was taken as an arbitrary cut-off to assess effectiveness of a drug as monotherapy. ER ≥ 2 indicated that there was greater than or equal to 1 fold difference in dilution between the MIC of the isolate and the breakpoint MIC value.

ER	P/T	C/S	T/C	Cpi	Czd	Dor	Mer	Imi	AK	G	Lev	Cip	Tig	Azt
1	2	2	32	5	1	7		33	4	1	4	3	2	7
2	45	53			35	11	14	23	2	8	23	2		36
4	9			31	15	10	6		2	53	29	56		5
8				23	7	9	36	2	55		3			
16						21					2			

Among the susceptible*P.aeruginosa* isolates, ER ranged from 1 to 16. The distribution of the isolates susceptible to each agent based on ER is shown in Table 1.

Table 1: The distribution of susceptible *P.aeruginosa* isolates based on Efficacy Ratio

P/T=Piperacillin/Tazobactam, C/S = Cefaperazone/ Sulbactam, T/C = Ticarcillin/ Clavulanate, Cpi = Cefepime, Czd= Ceftazidime, Dor = Doripenem, Mer= Meropenem, Imi = Imipenem, AK = Amikacin, G = Gentamicin, Lev = Levofloxacin, Cip = Ciprofloxacin, Tig = Tigecycline, Azt = Aztreonam.

ER	P/T	C/S	T/C	Cpi	Czd	Dor	Mer	Imi	G	Lev	Cip	Tig	Mn	Sxt
1	1	2		1	2					1		16	8	16
2	2	14	13	1	9					2	2	9		
4	9			8	2		2		17	2	10	17	23	
8				4	1	3	12	14				1		
16						11				8				

Among the susceptible isolates of *Acinetobacter baumannii-calcoaceticus* (ABC) complex also, the ER ranged from 1 to 16. The distribution of the isolates susceptible to each antimicrobial based on ER is shown in Table 2.

Table 2: The distribution of susceptible ABC complex isolates based on Efficacy Ratio

P/T=Piperacillin/Tazobactam, C/S = Cefaperazone/ Sulbactam, T/C = Ticarcillin/ Clavulanate, Cpi = Cefepime, Czd= Ceftazidime, Dor = Doripenem, Mer= Meropenem, Imi = Imipenem, G = Gentamicin, Lev = Levofloxacin, Cip = Ciprofloxacin, Tig = Tigecycline, Min = Minocycline, SXT = Trimethoprim-Sulfamethoxazole.

Discussion

In this era of antimicrobial stewardship, fine-tuning antibiotic selection for the treatment of critical conditionslike blood stream infections andfacilitating tochoose the most appropriate drug for each pathogen is the need of the hour. Choosing the drug with the lowest numerical MIC value is an incorrect approach to interpreting the susceptibility report. Calculating the efficacy ratio helps in defining the order of preference, as a drug with a higher value should be more effective than a drug with a lower value. It is also useful in predicting the best treatment option within and among the different classes of antimicrobials. Apart from parameters like MIC value and efficacy ratio, the site of infection, safety, ease of use and cost of each drug against specific organisms must also be considered while determining the optimum antibiotic(3).

In this study, on comparing the different classes of drugs for *P.aeruginosa* it is noted that carbapenem has the best activity. Among the carbapenems,with an efficacy ratio = 16, doripenem is distinctly better than the other members of the class. This is closely followed by meropenem with almost 45% of the isolates having an efficacy ratio = 8. While imipenem predominantly shows borderline activity with most isolates having an MIC value equal to the breakpoint MIC (efficacy ratio = 1). Thus the use of imipenem as a monotherapy against *P.aeruginosa* needs to be considered with caution(7).

The next class of drugs which showsconsistently good activity against *P.aeruginosa*is aminoglycosides with 2 – 4 fold difference in dilution between MIC of isolate and breakpoint MIC. Within the class, amikacin with an efficacy ratio = 8 is superior to gentamicin having an efficacy ratio = 4.

This is followed by fluoroquinolones, where both levofloxacin and ciprofloxacin have almost similar efficacies. However, levofloxacin is less consistent when compared to ciprofloxacin, with its efficacy ratios widely spread from 2 to 16. Therefore, ciprofloxacin appears to be a reliable choice of antibiotic among this group.

Among the cephalosporins, with efficacy ratio = 4 to 8, cefepime has an edge over ceftazidime. Though ceftazidime appeared to be a good alternative, it hasa

lower efficacy ratio = 2 with borderline activity against *P.aeruginosa,* hence cefepime is preferable.

All the β-lactam/ β-lactamase inhibitor combinations seem to have borderline activity. Piperacillin/tazobactam (72%)has a higher efficacy ratiothan cefaperazone/sulbactam (70%), while ticarcillin/clavulanate is not a good option in the treatment of *P.aeruginosa* infections since almost 59% of the isolates show resistance to the drug.

Aztreonam shows low activity and should not be considered as a single agent to treat infections caused by *P.aeruginosa.*

Among the different drugs tested for action against ABC complex, carbapenems show the most activity in this study. Doripenem has the highest efficacy ratio = 16 within the class. This is followed by meropenem and imipenem, both having similar efficacy ratio = 8 and are equally good choices for treatment.

Among the fluoroquinolones, it is noted that levofloxacin is better than ciprofloxacin for ABC complex with at least a 2 fold difference in dilutions. Most of the isolates susceptible to levofloxacin have an efficacy ratio = 16 while isolates susceptible to ciprofloxacin mostly have an efficacy ratio = 4.

The cephalosporins – cefepime and ceftazidime – have moderate efficacy against ABC complex compared to other classes of drugs.Cefepime is slightly better than ceftazidime. All the β-lactam/ β-lactamase inhibitor combinations have borderline action. And cefaperazone/sulbactam is seen to be marginally better than piperacillin/tazobactam and ticarcillin/clavulanate. Among the broad spectrum antibiotics, minocycline has better action than tigecycline against ABC complex with an efficacy ratio = 4.

Furthermore, ER can be used as an important tool to decide on monotherapy or combination therapy. For this, we hypothesize that drugs with an efficacy ratio ≥ 2 would work well as monotherapy and agents with an efficacy ratio < 2 should be preferred as combination therapy for better outcomes. This study further needs to be correlated clinically. When conducted, clinical studies will help choose the efficacy ratio cut-off for monotherapy and combination therapy.

To summarize, on assessing the effectiveness of various classes of antimicrobials against both *P.aeruginosa* andABC complex, carbapenems, particularly doripenem emerged as the best choice of treatment for both the organisms. However, both meropenem and imipenem are equally good against ABC complex, meropenem has an upper hand over imipenem against *P.aeruginosa*. Similarly, cefepime also has an edge over ceftazidime, not only among the *P.aeruginosa* isolates but also in ABC complex isolates. β-lactam/ β-lactamase inhibitor combinations have borderline activity against both the organisms.Among the fluoroquinolones, ciprofloxacin is more consistent against *P.aeruginosa* and levofloxacin is distinctly better for ABC complex. Tigecycline has no activity against *P.aeruginosa*, however it is a good option for infections caused by ABC complex.

Conclusion

The calculation of efficacy ratio is essential for accurate and meaningful interpretation of an antimicrobial susceptibility report. Additionally, the order of preference of antibiotics for treatment and their use as monotherapy or combination therapy can be predicted. This right approach will reduce morbidity and mortality and is an important tool in antimicrobial stewardship.

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