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Research Article

Antibacterial Therapy Used in the Treatment of Bloodstream Infections Caused by Methicillin-Sensitive and Resistant *Staphylococcus aureus*

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Abstract

Methicillin-susceptible *Staphylococcus aureus* or methicillin-resistant *Staphylococcus aureus* (MSSA or MRSA) sensitive or resistant to oxacillin are the main causative agents of bloodstream infection (BSI) and are associated with high rates of morbidity and mortality worldwide. The aim of the present study was to analyze the frequency of MSSA and MRSA isolates recovered from patients with BSI and to evaluate the main antibacterials used in the treatment. We retrospectively evaluated data from 98 patients who had BSI (22 MRSA BSI and 76 MSSA BSI) hospitalized in different sectors of a hospital between 2013 and2021. The 98 *S. aureus* isolates evaluated were sensitive to vancomycin, linezolid, gentamicin, daptomycin, teicoplanin and rifamycin. The median length of stay was 27.5 and 19 days for patients with MRSA BSI and MSSA BSI, respectively. The mean number of antibacterials used per patient was approximately 5 for patients with MRSA BSI and 6 for patients with MSSA BSI. In the analysis of the antibacterial therapy used before and after the detection of MSSA BSI and MRSA BSI, we observed that most patients were already on the appropriate antibacterial therapy or had their therapy adjusted after detection. For patients with MRSA BSI, adjustment was performed mainly with vancomycin or linezolid. For patients with MSSA BSI, the therapeutic adjustment was performed using oxacillin, vancomycin and linezolid. In relation to patients who had MRSA BSI, in 7 of them other bacteria were isolated from the urine, catheter tip, endotracheal aspirate and/or blood. Of these patients, only 2 survived (29%). However, of the 11 patients who had only MRSA infection, 9 survived (82%). Our data suggest that the simultaneous presence of *S. aureus* and other bacteria may lead to worse clinical outcomes. We also evidenced a high consumption ofantibacterials per patient and that although the median length of stay was higher for patients with MRSABSI, the average use of antibacterials was slightly higher in patients with MSSA BSI. Thus, we conclude that there is a need to improve the management of antibacterial therapies, diagnostic methods and measures to control and prevent BSI by MRSA and MSSA.

Keywords: *Staphylococcus aureus*; MSSA and MRSA; Bloodstream Infection; Co-infection; Antimicrobials

Abbreviations

S. aureus: Staphylococcus aureus; MSSA: Methicillin-sensitive *Staphylococcus aureus;* MRSA: Methicillin- Resistant *Staphylococcus aureus*; BSI: Bloodstream Infection; PBP: Penicillin-binding Protein; *SCCmec*:Staphylococcal Cassette Chromosome mec*;* MSSA BSI: Methicillin-sensitive *Staphylococcus aureus* Bloodstream Infection; MRSA BSI: Methicillin-resistant *Staphylococcus aureus* Bloodstream Infection; SXT: Sulfamethoxazole-Trimethoprim

Introduction

Staphylococcus aureus, Gram-positive cocci, has been found colonizing the skin and mucous membranes of 40% of individuals. According to the sensitivity profile to either oxacillin or methicillin, *S. aureus* isolates can be classified as sensitive known as methicillin-susceptible *Staphylococcus aureus* or methicillin-resistant *Staphylococcus aureus* (MSSA or MRSA). This pathogen has great clinical importance acting as an agent of simple to potentially fatal infections as in the case of bloodstream infection (BSI). The incidence of bacteremias is high and can range from 3 to 50 cases per 100,000 people per year, globally [1,2]. Current data indicate considerable rates of 20 to 25% of mortality attributed to BSI by MRSA and MSSA worldwide [3].

BSI is characterized by the presence of a microorganism in one or more blood culture samples, which when not treated correctly can lead to sepsis and death [4]. This infection can be acquired in environments related to health care or the community, with *S. aureus* being one of the main causative agents of this infection. Several factors may be involved in the development of this infectious condition, such as the use of invasive devices, age of patients, type of hospitalization unit, clinical manifestations, comorbidities and immunosuppression [4,5].

It is well established that MSSA strains have a broad sensitivity to most antibacterials, including the group of antistaphylococcal penicillins. MRSA isolates, on the other hand, are often multi-resistant andin addition to resistance to β-lactams may also present resistance to antibacterials of different classes. The main mechanism for resistance to oxacillin in *S. aureus* is the production of an altered penicillin binding protein (PBP), with low affinity to all β-lactams, encoded mainly by the *mec* gene. Its wide dissemination occurs by mobile genetic elements called staphylococcal cassette chromosomes (*SCCmec*) [5,6].

The antibacterial treatment of choice in MSSA BSI is based on the class of β-lactams, especially oxacillin. As for MRSA BSI, the first-line of treatment is usually performed by the administration of vancomycin or daptomycin. In the absence or contraindication of drugs to treat MRSA BSI, other antibacterials such as linezolid and ceftaroline are therapeutic options aiming at achieving therapeutic success, increased survival, absence of symptoms and microbiological eradication [7].

Currently, there is still a lack of information that can guide to a more targeted and effective antibacterial treatment for *S. aureus* BSI [8]. According to Hollandet., *et al*. less than 2,500 patients have been included in randomized clinical trials published for *S. aureus* BSI in the last 20 years and less than 450 in the search for MRSA BSI. Thus, our study evaluated the frequency of MSSA and MRSA isolates recovered from patients with BSI and the main antibacterials used in empirical and targeted treatment, in addition to their relationship with the clinical outcome of these patients. In general, we observed the need to improve antibacterial therapies, clinical diagnosis, and also measures to control BSI by MRSA and MSSA.

Materials and Methods

The present study is a retrospective study that evaluated clinical isolates of *S. aureus* MRSA and MSSA recovered from patients diagnosed with BSI, hospitalized between 2013 and 2021 in a teaching hospital. The hospital is located in southern Brazil, an institution that offers general and advanced medical diagnostic services, aimed at the care of the local and regional population.

The general and clinical data of the patients were acquired through the electronic medical records platform (GSUS). The identification of bacteremia and the sensitivity profile of the antimicrobials tested were obtained through automated equipment BACTEC™ and Phoenix™ (BD Diagnostic Systems, sparks, MD), respectively. Inclusion criteria were: patients ≥ 18 years, of both sexes and with a positive diagnosis of BSI by MRSA or MSSA.

The data obtained were analyzed by SPSS (Statistics), version 23.0 for Windows (IBM Corporation, Amonk, NY, USA) and Minitab®-18 (Statistical Software). To identify the occurrence of MRSA and MSSA infection, it was evaluated using Student's t-test or chi-square test for categorical variables. The data wereconsidered significant when the variables presented a value of $p < 0.05$. The variables analyzed were gender, age, initial diagnosis, inpatient unit and clinical outcome.

The study was approved by the Research Ethics Committee of the State University of Maringá (approval number 2.093.342/CAAE 63610816.0.0000.0104 and approval number 4.808.018/CAAE 47908021.9.0000.0104).

Results and Discussion

The use of appropriate therapy has been one of the main objectives of clinicians when treating BSI mainly, associating shorter hospital stay and recurrence of infection [9,10]. The use of empirical broad- spectrum antibacterials has been constant in most infecti-

ons. However these drugs can quickly lose their activity due to their exaggerated use. This is quite obvious to observe, even during the COVID pandemic, as the excessive use of antibacterials has led to the spread of resistant strains [11]. In the present study, it was found that the use of antibacterials was higher in the MSSA BSI group compared to the MRSA BSI group, which alerts to the fact that even with sensitive isolates we are maintaining unnecessary antibacterials not performing the necessary de-escalation.

In the study period, a total of 147 patients had bacteremia caused by *S. aureus*. Among these patients, 98 were initially analyzed (22 with MRSA BSI and 76 with MSSA BSI). The exclusion of the 49 patients in this study was due to the absence of data on the therapy used or difficulty in accessing data from physical records that have not yet been digitized.

From the analysis of the variables, it was found that there was no distinction between gender, age, initial diagnosis and clinical outcome for patients who had BSI due to MRSA and MSSA.

In the analysis of the variable inpatient unit, it was observed that in the emergency room, the BSI were mainly caused by MSSA ($p < 0.014$) and in the medical clinic, most BSI were caused by MRSA ($p < 0.045$). Although the Intensive Care Unit is the sector with the highest prevalence of resistant bacteria, in our study, as well as in a Hospital in the capital of Minas Gerais, Brazil, the medical clinic was the most important hospital unit for patients with MRSA BSI [12,13].

Table 1 shows that the 98 *S. aureus* isolates evaluated, regardless of sensitivity to oxacillin, were sensitive to vancomycin, linezolid, gentamicin, daptomycin, teicoplanin and rifamycin. We also found that MRSA clinical isolates showed sensitivity mainly to tetracycline (100%), minocycline (95.5%), tigecycline and sulfamethoxazole-trimethoprim (SXT) (90.9%).

	MSSA (n = 76)				MRSA (n = 22)			
Antimicrobials	**N**	**S %**	**I %**	**R %**	**N**	**S %**	**I %**	**R %**
Oxacillin	76	100	0	0	22	0	0	100
Vancomycin	76	100	0	0	22	100	0	0
Ceftaroline	40	100	0	0	5	80	0	20
Ciprofloxacin	75	77.3	20	2.7	21	23.9	14.3	61.8
Chloramphenicol	62	53.2	0	46.8	4	50	0	50
Clindamycin	17	94.1	0	5.9	20	35	0	65
Trimethoprim-sulfamethoxazole	75	98.7	0	1.3	22	90.9	0	9.1
Linezolid	76	100	0	0	22	100	0	0
Tigecycline	74	100	0	0	22	90.9	0	9.1
Erythromycin	76	48.7	1.3	50	22	9.1	4.5	86.4
Gentamicin	15	100	0	0	4	100	0	0
Daptomycin	76	100	0	0	22	100	0	0
Minocycline	73	100	0	0	22	95.5	4.5	0
Penicillin	66	1.5	0	98.5	22	0	0	100
Teicoplanin	18	100	0	0	4	100	0	0
Rifampin	60	100	0	0	18	100	0	0
Tetracycline	35	91.4	2.8	5.8	16	100	0	0
Quinupristin-dalfopristin	36	100	0	0	0	0	0	0

Table 1: Antimicrobial susceptibility profile of 98 methicillin-susceptible and methicillin- resistant *Staphylococcus aureus* (MSSA and MRSA) isolates recovered from patients with bloodstream infection.

MSSA= methicillin-susceptible *Staphylococcus aureus*; MRSA= methicillin-resistant *Staphylococcus aureus*; n= total number of isolates for each methicillin resistance category; N= number of isolates; S %= percentage of susceptible isolates; I %= percentage of intermediate isolates; R %= percentage of resistant isolates.

Over the past 40 years, antimicrobial resistance, particularly resistance to β-lactams, has been impacting antibacterial therapy. Older drugs such as SXT, because they are little used, have shown activity against MRSA isolates. In our study, 9.1% of MRSA isolates were resistant to SXT, which indicates that this antibacterial may be a great therapeutic option, including empirical treatment. Ac-

cording to Nurjadi., *et al*. [14], SXT is little used; however it is a low-cost therapeutic option and presents few side effects. Another group that has been shown to be effective is ceftaroline, a fifth-generation cephalosporin, and has binding affinity for both PBP and PBP2a, thus justifying its activity for both MSSA and MRSA [15]. In our study among MSSA isolates, sensitivity to this drug was 100%, but among MRSA isolates, although only 5 isolates were tested, 20% were resistant.

Of the 98 patients selected for the study, 22 had MRSA bacteremia. However, due to the lack of complementary data, only 18 of the 22 patients were evaluated and included in the schematic representation of the cases (Figure 1). The mean age of the 18 patients was 69 years, with a predominance of males (72% - 13/18) and a median hospitalization period of 27.5 days. In 39% of patients (7/18), in addition to MRSA, other bacteria were isolated in urine, catheter tip, endotracheal aspirate and/or blood.The most isolated bacteria were *Klebsiella* pneumoniae (P4, P6, P7 and P15), *Acinetobacter baumannii* (P8,P16 and P17) and *Pseudomonas aeruginosa* (P9 and P17). Of the 7 patients who also had infections by other microorganisms, only 2 survived (29%). On the other hand, of the 11 patients who had only MRSA infection, 9 survived (82%) (Figure 1). In a previous study, Dambroso., *et al*. [11] showed 41 patients with COVID-19, from whom carbapenemase-producing *K. pneumoniae* isolates were recovered. Of the 41 patients, 5 also had *S. aureus* infection and only 40% (2/5) of the patients survived. These data suggest that the simultaneous presence of *S. aureus* and other bacteria may lead to worse clinical outcomes in patients with or without COVID-19. The impact of co-infections is greatly underestimated and still needs to be better elucidated, especially with regard to pathogenesis, diagnosis and treatment [16].

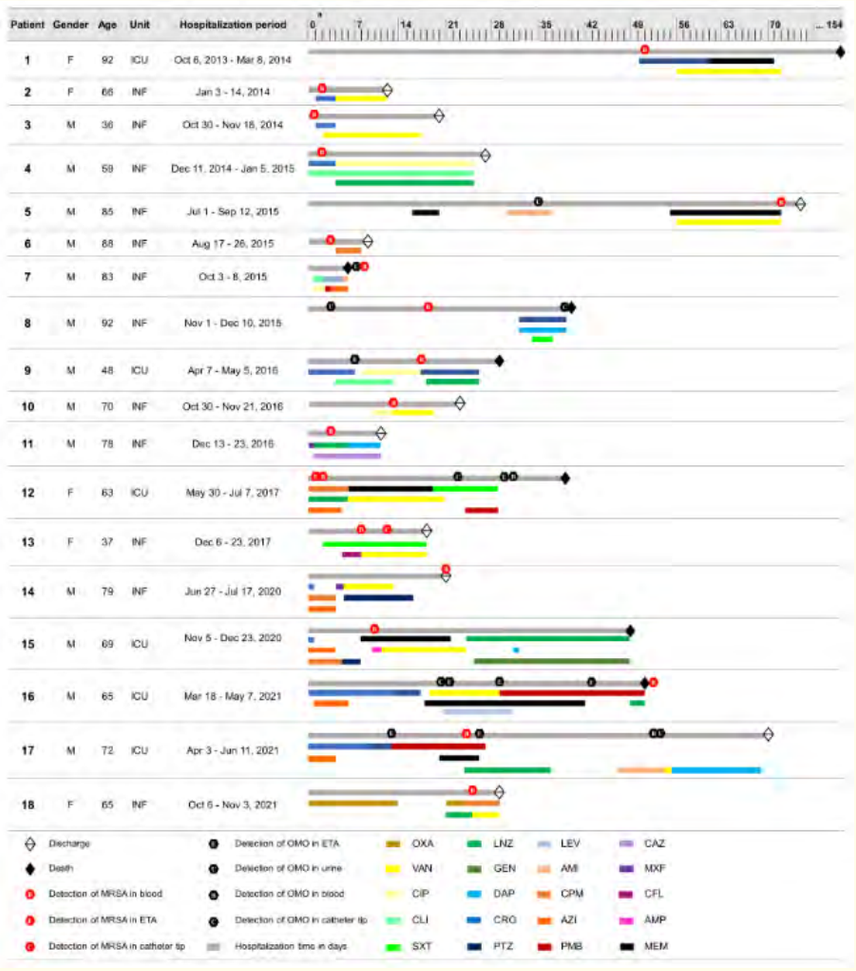

Figure 1: Schematic of cases of hospitalization time in days.

Note. ICU, Intensive-Care Unit; INF, infirmary; M, male; F, female; ETA, Endotracheal aspirate; OXA, oxacillin; VAN, vancomycin; CIP, ciprofloxacin; CLI, clindamycin; SXT, trimethoprim-sulfamethoxazole; LNZ, linezolid; GEN, gentamicin; DAP, daptomycin; CRO, ceftriaxone; PTZ, piperacillin + tazobactam; LEV, levofloxacin; AMI, amikacin; CPM, cefepime; AZI, azithromycin; PMB, polymyxin B; CAZ, ceftazidime; MXF, moxifloxacin; CFL, cephalixin; AMP, ampicillin; MEM, meropenem; MRSA, Methicillin-resistant Staphylococcus aureus; OMO, Other microorganisms: *Klebsiella pneumoniae* (P4, P6, P7, P15); *Acinetobacter baumannii* (P8, P16, P17); *Pseudomonas aeruginosa* (P9, P17); *S*. coagulase-negativo (P12); S. *haemolyticus* (P16); *S. epidermidis* (P12); *Stenotrophomonas maltophilia* (P12); *Burkholderia* sp. (P16); *Enterococcus faecium* (P17).

During the hospitalization period, the average number of antibacterials used per patient was approximately five. Of the 18 patients, 2 died before MRSA was identified and 16 patients were either already on appropriate antimicrobial therapy (1 patient) or had their therapy adjusted after MRSA was detected (15 patients). The adjustment was mainly performed with pure vancomycin or linezolid or combined with other antimicrobials. Of the 5 patients who received vancomycin alone, 4 survived (80%) and of the 5 patients who received vancomycin in combination, 3 patients survived (60%). Pure vancomycin was the therapy chosen mainly in cases of MRSA-only infection and combined vancomycin in cases of simultaneous infection with MRSA and other microorganisms. Only 1 patient was treated with pure linezolid, which survived and of the 4 patients who were treated with linezolid in combination, 2 patients survived (50%).

Vancomycin or daptomycin remained the first choice antibacterial in MRSA BSI monotherapy according to the Infectious Diseases Society of America (IDSA) [17]. According to Tsaiet., *et al*. [18] linezolid can alsobe used if the MRSA BSI originates from pneumonia. Other options such as ceftaroline may help in the treatment of MRSA BSI, but in many hospitals, as well as in this study, there is still no approval or standardization for obtaining this antibacterial even with the presence of resistance as demonstrated in our research. A study conducted by Tong., *et al*. [19] pointed out several studies where it analyzed the synergy with various classes of antibacterials and monotherapy against MRSA BSI which did not obtain satisfactory clinical results. A combination of analyzed drugs were associated with increased toxicity and worse clinical outcomes, in line with the data we obtained in this research with therapy mainly combined with antibacterials of the β-lactam class (Figure 1).

In relation to the 76 patients who had MSSA BSI, the analysis of the antibacterial treatment was performed on 31 only due to the difficulty in obtaining the treatment data of the other patients. The median hospitalization period of the 31 patients was 19 days and the average use of antibacterial used per patient was approximately 6 days, with the concomitant use of a maximum of three antibacterials (Figure 1).

In the analysis of antimicrobial therapy used before and after the detection and identification of MSSA BSI, we observed that 74% (23/31) of patients had adjusted treatment. The therapeutic adjustment was mainly performed using oxacillin (57%- 13/23), vancomycin (22%- 5/23) and linezolid (22%- 5/23).Among these patients, 74% (17/23) were discharged. Eight patients did not have their therapy adjusted, after identifying MSSA only 50% (4/8) were discharged (Table 2).

Patient	HT	Empiric antimicrobial therapy	Antimicrobial therapy afteridentification of MSSA	Outcome
P19	16	CRO, CLI	CRO, CLI	Discharge
P20	46	CPM, CLI. CAZ	OXA, CAZ, CLI	Discharge
P21	7	-	OXA, CRO	Discharge
P22	21	CRO, CLI, AMP	CRO, OXA, AMP, CLI	Discharge
P23	19	CRO, CLI	CRO, CPM, OXA, CLI	Death
P24	79	CRO, AMP, PTZ, TGC, LNZ, IMP, SXT, PMB, VAN	OXA, VAN	Discharge
P25	30	-	CAZ, OXA, PMB, LNZ	Death
P26	74	CPM, CRO	CRO, OXA, PTZ, MEM, TGC, LNZ	Discharge
P27	14	CRO	CRO	Discharge
P28	16	CRO	CAZ	Discharge
P29	22	CAZ	CAZ	Discharge
P30	3	CRO, CLI	OXA, CLI	Death
P31	32	CRO, CLI, AZI, VAN	CIP	Discharge
P32	60	CFZ, PTZ, VAN	PTZ, MEM, CPM, VAN, LNZ, ERY, PMB, TGC	Discharge

P33	9	CRO, AZI	OXA, GEN	Discharge
P34	13	CRO	OXA	Discharge
P35	5	CRO	CRO	Death
P36	9	CRO, CAZ, CIP	CPM, OXA, PTZ, CAZ, VAN, CIP	Death
P37	13	CLI, CAZ	CLI, CAZ	Discharge
P38	29	PPT, CRO, AZI	CRO, PTZ, AZI	Discharge
P39	17	CRO, AZI	PTZ, OXA, MEM, CRO, AZI	Death
P40	56	CRO, PPT, MEM, LNZ	LNZ, AMI	Discharge
P41	11	CRO, AZI	CRO, AZI	Discharge
P42	21	CRO, CIP, OXA	OXA, PTZ, CIP, LNZ	Discharge
P43	11	OXA, CRO, CLI, PTZ, VAN	PPT, CRO, CLI, VAN	Death
P44	61	CRO, AZI, PTZ, MEM	MEM	Death
P45	18	CRO, CLI	OXA, CRO, CLI, GEN	Discharge
P46	72	CRO, OXA, CPM, LNZ	OXA, CPM, MEM, AMP, VAN, AMS, PMB, TGC	Discharge
P47	29	CFL, CRO, CIP, OXA	OXA, CIP	Death
P48	9	CRO, PTZ, OXA	CRO, OXA, PTZ	Death
P49	59	CRO, AZI, PTZ, MEM, PMB, SXT, VAN	MEM, VAN, LNZ, PMB, COL	Discharge

Table 2: Antimicrobial prescriptions before and after detection and identification of methicillin-sensitive *Staphylococcus aureus*. HT, hospitalization time in days; MSSA, methicillin-sensitive *Staphylococcus aureus*; OXA, oxacillin; VAN, vancomycin; CIP, ciprofloxacin; CLI, clindamycin; SXT, sulfamethoxazole-trimethoprim; LNZ, linezolid; GEN, gentamicin; CRO, ceftriaxone; PTZ, piperacillin-tazobactam; AMI, amikacin; CPM, cefepime; AZI, azithromycin; PMB, polymyxin B; CAZ, ceftazidime; CFL, cephalexin; AMP, ampicillin; MEM, meropenem; ERY, erythromycin; TGC, Tigecycline; COL, colistin, IMI, imipenem; AMS, ampicillin-sulbactam.

According to the study by La., *et al*. [20], MSSA BSIs continue to negatively impact high morbidity and mortality rates worldwide. The main guidelines recommend both the treatment of first choice as well as the replacement of empirically prescribed antibacterials after the identification of the MSSA clinical isolate by antibacterials of the β-lactam antistaphylococcal class.

Some health institutions still choose to maintain empirical prescriptions of glycopeptide class antibacterials, even in a scenario with low prevalence of MRSA and also after confirmation of the microbiological report of sensitive isolate for patients with severe diseases, certain comorbidities, possibility of difficult–to-treat metastatic infections and eventual allergies to penicillin. However, some studies confirm the disadvantage of using the glycopeptide class as the first choice antibacterial to treat MSSA BSI compared to β-lactamic antistaphylococcal antibacterials in terms of patient survival [20,21]. Antibacterial therapy of MSSA BSI with glycopeptides is associated with increased mortality, and may be related to slower bactericidal activity of these antibacterials, resulting in persistent BSI and also the possibilities of side effects such as nephrotoxicity, mainly by the use of vancomycin. The insecurity in theadequate prescription of antibacterial drugs, and especially the de-escalation of glycopeptides, can directly impact the clinical outcome of patients, calling for the need for more scientific studies and enabling the transfer of more information to prescribers. The data from our study corroborate with these, as the greater use of antibacterials in the MSSA BSI was verified, as well as the maintenance of glycopeptides with high mortality [20,21].

Conclusion

This study showed a high consumption of antibacterials per patient regardless of the amount of clinical isolates presented during the hospitalization period. Unfortunately, the practice of escalation that would boost a more targeted and appropriate therapy was little used, which kept the financial costs high despite the sensitivity of the isolates. The use of appropriate empirical antibacterials favored the outcome of hospital discharge mainly in patients with single *S. aureus* infections without another microorganism. We recommend that MSSA BSI reports be treated with targeting the sensitive isolate, thus enabling a reduction in the number of prescribed antibacterials and consequently bacterial resistance. This clinical practice, in addition to improving the clinical outcome of patients, can significantly reduce the costs of public health services.

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Conflict of Interest

None declared.

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