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Cost minimization analysis on IV to oral conversion of antimicrobial agent by the clinical pharmacist intervention

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ABSTRACT

Antimicrobial agents are used to treat the infectious diseases which and has become a routine milieu. Prescribing intravenous (IV) antimicrobial agents are needed for abruptly subduing the infectious stage and will leads to decrease the infectious severity of the patient. The cost minimization Analysis involved monitoring the IV to oral conversions carried out in General Medicine department as a part of Antimicrobial stewardship Programme (ASP) for initial 3 months followed by feedbacks, guideline preparation and CME programs as intervention. This was followed up by a post-intervention audit to assess the effectiveness of the interventions performed. An aggregate of 102 subjects were enrolled in the study and quantitative use of the parenteral AMA was found to be significantly reduced in the post-interventional phase in comparison to the pre-interventional phase ($p = 0.028$) and the conversion per patient rate is also increased ($p = 0.0001$). Similar reductions were also achieved by the intervention in the duration required for oral conversions, average difference is 2 days ($p = 0.000$). 19.5% reduction in the usage of cost of antibiotics is achieved with a 0.010076DDD/100 Bed days difference to the control population. The study was successful in increasing the conversion rate which clearly implicated the acceptance of guideline. The recommendations of the clinical pharmacist were successful in reducing both the length of stay and duration of parenteral therapy, there in reducing the consumption and cost of antimicrobial therapy. The cost minimizations were found by IV to oral conversion of antibiotics without any change in the treatment outcome.

1. Introduction

Infectious diseases have become a common entity in the current society and have positively influenced enhanced use of antimicrobial agents (AMA). Initiating therapy with intravenous (IV) antimicrobial agents is necessary for the control of severity of the infection of the patient from the life-threatening complications; but the prolongation of I.V therapy after the severity reduction of the patient is not a necessity in all the cases. Prolongation of I.V administration can prove to be discomfort for the patients and may culminate in non-compliance as well as injection related problems such as secondary infections. Therefore, the prudent conversion of intravenous to oral AMA agents is vital from the patient perspective to reduce the inconvenience and economic burden associated with the therapy.[1]

Antimicrobial stewardship Programme (ASP) is a rational, systematic approach to the use of antimicrobial agents in order to achieve optimal outcomes – those of the patient and of the larger population. The patient outcome includes the reduction in the consumption and the larger population outcome to target the antimicrobial resistance.[2] IV to PO conversion of antimicrobial agents is one of the key strategies in the ASP and is considered in local and national programs to prevent the emergence of antimicrobial resistance and decrease preventable healthcare associated infection. The IV to PO conversion key strategy in the antimicrobial stewardship programme.[3]

Intravenous to oral conversion practice can effected through 3 methods of which the first one is termed as “Sequential therapy” and refers to the act of replacing a parenteral version of a medication with its oral counterpart of the same compound. The second one, called as “Switch therapy”, involves the conversion of an IV medication to an oral equivalent; within the same class and with same level of potency, but of a different compound. The third modality is termed “Step down therapy” in which an injectable medication is substituted with an oral agent in another class or, a different medication within the same class where the frequency,

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dose, and the spectrum of activity may not exactly be similar.[1] The factors contributed for the emergence of this strategy are newer concepts on IV as well as PO antimicrobial pharmacodynamics, advent of newer, potent, broad-spectrum oral agents achieve higher consistent serum and tissue concentrations, and availability of randomized clinical trials comparing various IV and oral therapeutic strategies.[4]

A large number of comparative clinical trials have been performed; randomizing patients between IV or oral therapy for the entire treatment course; and IV therapy for a few days followed by oral therapy.[5,6] All studies have reported equal efficacy with the two treatment strategies. Many contemporary reviews have therefore concluded that the evidence available clearly supports the use of 'early switch therapy'. [4,7,8] Antibiotic use can be optimized by earlier conversion from IV to oral therapy which imparts the following advantages such as reduction of injection related pain, skin reactions, hematoma and benefit in the money as well as labor cost.[9,10] World Health Organization (WHO) reported that the irrational use of medicines is a global phenomenon that burdens the patient and healthcare system.[11] Overuse of injections when oral formulations would be more appropriate is one of the key factors for the irrational use of medication use. Hence IV to oral conversion within a specified time is one of the major aspects to improve the rational antibiotic use. Moreover, once the culture and sensitivity reports are available, IV to oral conversion enables one to select a cheaper or older antibiotic, which is as effective as the IV antibiotic.[12] A common misconception among physicians is that bioavailability of IV medications is always higher than that of their oral counterpart, and use of the former can produce a prompt symptomatic relief.[13] Paradoxically, a large array IV of drugs has been estimated to produce equivalent plasma concentrations irrespective of IV or oral use. Another such notion is that administration of the entire regimen of parenteral antibiotics is more efficacious in preventing relapses during the therapeutic course.[14]

There is general consensus that the best way to accomplish rapid onset of drug action is by creating an instant therapeutic blood level by administering the drug IV. However, for sustained use, this approach requires establishing indwelling IV access, usually in a hospital setting.[15,16]

Only a few studies demonstrating the effect of implementing switch criteria in a general population of medical patients have been identified of which majority were conducted in developed countries such as UK,[17] USA,[18] Netherlands,[19] Switzerland[20] and Norway. [9] It is notable that none of these studies have assessed the long term sustainability of guideline implementation when a pharmacist is not actively integrating switch therapy in the medical wards on a routine basis.[21]

The cost minimization analysis (CMA) measures and compares the input cost, and assume outcome to be equivalent. If two therapies are considered clinically equivalent, then only the costs of the interventions need to be considered. The acceptability of the CMA study is based on the reader's acceptance of the equivalency of the two compared population's outcome.[22]

The defined daily dose (DDD) used to equate the outcome of the study. "The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults." A DDD will only be assigned for drugs that already have an Anatomical Therapeutic Chemical (ATC) code. Drug consumption figures should preferably be presented as numbers of DDDs/1000 inhabitants/day or, when in-hospital drug use is considered, as DDDs per 100 bed days.[23] The AMC (Antimicrobial consumption) tool 2014 is windows based software for the determination of antibiotic consumption developed by the Arno Muller, partly supported by the European centre for Disease prevention control (ECDC).[24]

The current study was aimed at assessing the conversion of parenteral antimicrobial agents to oral antimicrobial agents before and after clinical pharmacist intervention and study the impact of the same on the prevailing prescribing practices.

2. Methodology

Tertiary care **350** bedded referral hospital in the Malappuram district, Kerala, was the study setting and the approximate strength about 180 in- patients/day. The study was conducted over the duration of 7 months from April to September 2016. Patient population was limited to those who have prescribed with parenteral antimicrobial agents in the general medicine department of the hospital. There is no restriction for any of the infectious disease, only the antimicrobials and their conversion are only taken into account. The patients who are shifted from the other departments are excluded from this study. The study protocol was approved by the Institutional ethical committee through letter numbered IEC/ASH/2014.

In this study design, the recommended sample size was estimated with proportional risk difference null hypothesis of the equally distributed large population. Because of the zero recommendations in the pre interventional period proportions selected 0.2 and 0.8 for the pre and post interventional group with risk difference of 0.6. With the imagination of intervention will make a difference in the therapy the power is kept as 95 with an error of 0.5 were given the population size as 24 for the each hand.[25,26]

The prospective cost minimization analysis interventional study was divided into 3 phases with the initial 3 months constituting pre interventional, followed by 1 month of

DATA COLLECTION TOOL								
PATIENT DEMOGRAPHICS					DATE			
INFECTIOUS STATUS OF THE PATIENT		FABRILE ☐ AFEBRILE ☐	BP FLECTUATION	YES ☐ NO ☐	ORAL INTAKE	YES ☐ NO ☐	OTHER NON COMPELLING FACTORS	.....
SERIAL NO:	ANTIMICROBIAL AGENT	DOSE	ROUTE	FREQUENCY	COST OF DRUG	DDD	START & STOP DATE	DAYS FOR CONVERSION
RECOMMENDATIONS								

Fig. 1. Data collection tool.

interventional phase and last 3 month representing the post interventional period. The data collected by the ward round participation with the physician well as review of the individual medication chart of the patient. The data collection were facilitated by the aid of a developed data collection form consisted of number of antimicrobial agents, duration of the therapy, number of conversions and the number of days taken for the conversions.

The intervention was associated with the antimicrobial stewardship programme. Because of the unavailability of an institutional IV to oral conversion guideline, guidelines were developed (Fig. 1) and got approved by the general medicine physician. The data for the guideline preparation was collected from the existing healthcare IV to Oral conversion guidelines and the drug information resources.[27–35] The new protocol is required because; all of the existing guidelines did not give the adequate data for the conversions. The IV to oral conversions were made those who have the conversion favourable conditions such as absence of fever, normal blood pressure(BP), consciousness and ability to take drugs orally were used as parameters for deciding the congruousness of the IV to PO conversions and making recommendation to physicians (Fig. 2).

The antimicrobial agent consumption were accessed in the form of DDD/100 bed day as a standard parameter for the equating the outcome and the same was calculated by using Antimicrobial Consumption Tool (AMC. All the statistical analysis was carried out using Statistical Package for Social Sciences (SPSS) software version 16.0 for operating system "Windows". The data under the each category were subjected to Chi square test for finding significant difference/association between categorical dependent variables with respect to various groups. P –value less than 0.05 is considered to be statistically significant.

3. Results

Comparing with the recommended sample size (n = 24) the population was found to be 52 and 50 for the pre and post interventional period respectively. Patient demographics such as gender and age are in almost equal proportion in the both study groups. The male population is 29% to 26% in the pre and post stage 23% to 24% are females. Similarly age group were found to be 42–52% are geriatrics and 56-48% are adults for the pre and post interventional stage with an exception of 2 pediatric patients in the pre interventional period. The current study is considered to be a CMA, so these factors are not taken into the account because the hypothesis described as the conversion to oral form will not made any decrease in the clinical efficacy.

The primary intervention, rates of IV to PO conversion was increased in the intervened population. In the both groups 80–84% of the population treatment was initiated with parenteral therapy in the study, in which only 5.76% (n = 3) of the population were performed conversion were as 72% (n = 36) of the patient had underwent conversion in the interventional period. For the 13.46% (n = 7) and 16% (n = 8) of the pre and post group had unfavorable condition for the conversion of the therapy such as fever spikes, fluctuations in the BP and the infection severity (Table 1). Condition for the conversion satisfied patients are 86.54% (n = 45) and 84% (n = 42) in the pre and post group, there is no conversions were performed for 42 patients in the pre interventional group were as for 36 patients conversions were made. There is a statistically significant difference (p = 0.0001) in the conversion rate was made by the active intervention of the clinical pharmacist.

Table 1
Iv to oral conversion undervent population.

IV TO PO Conversion	Intervention	
	Before	After
Un favored Population	7(13.46%)	8(16%)
No Conversion	42 (80.76%)	6 (12%)
Conversions	3 (5.76)	36 (72%)

CONVERSION GUIDE LINE FOR ANTIMICROBIAL AGNETS			
IV FORM	ORAL FORM	IV FORM	ORAL FORM
SEQUENTIAL THERAPY		SWITCH THERAPY	
LEVOFLOXACIN	LEVOFLOXACIN	CEFTAZIDIME	CIPROFLOXACIN
CIPROFLOXACIN	CIPROFLOXACIN	CEFAZOLIN	CEPHALEXIN OR CLOTRIMAZOLE
FLUCONAZOLE	FLUCONAZOLE		
METRONIDAZOLE	METRONIDAZOLE	CEFOTAXIME	CIPROFLOXACIN
CLINDAMYCIN	CLINDAMYCIN	AMPICILLIN SULBACTAM OR AMOXICILLIN CLAVULANATE	LEVOFLOXACIN + METRONIDAZOLE OR AMOXICILLIN CLAVULANATE
CLOTRIMAZOLE	CLOTRIMAZOLE		
AMOXYCILLIN	AMOXYCILLIN		
CEPHAZOLIN	CEPHALEXIN OR CEFUROXIME	IMIPENEM/ CILASTATIN	CIPROFLOXACIN + METRONIDAZOLE
		STEP DOWN THERAPY	
MOXIFLOXACIN	MOXIFLOXACIN	CEFTRIAXONE	CEFIXIME
FLUCLOXACILLIN	FLUCLOXACILLIN		
AMPICILLIN*	AMPICILLIN	Sequential therapy: Similar bioavailablilty Switch therapy: same class with Similar spectrum Step down therapy: Same class with different sprectrum. *Characterized by time over MIC principle	
CEFUROXIME*	CEFUROXIME		
ERYTHROMYCIN*	ERYTHROMYCIN		
AZITHROMYCIN*	AZITHROMYCIN		

Fig. 2. Conversion guideline for antimicrobial agents.

The intervention also made a difference in the use of parenteral AMA therapy when the patient are got discharged. Initially 21.15% (n = 11) of the population are discharged with parenteral antibiotics were as in the post interventional period that were reduced to 6% (n = 3). Even if the patients are eligible for the conversion, when the antibiotics are started just prior to the discharge date the physicians are forced to continue the parenteral formulations. Because of the recommendations for the conversion in the individual patient 15.15% reduction were achieved in the post interventional phase. 42.85% parenteral of the parenteral drugs were converted in 36 patients out of 84 drugs prescribed. Patient who had more than two parenteral agents are very hard satisfy the criteria because of the infection severity. But compared to the pre interventional period the significance of conversion is much higher in the post interventional period (p = 0.028) (Table 2).

The average days of parenteral therapy is continued for 3.66days(∼4days) were as in the post interventional stage the IV therapy is only prolonged for 2.45days(∼2days). A significant reduction (p = 0.0001) in the days taken for conversion were achieved. Conversion within 1 day is increased for 1.92% to 14% in the interventional group. The head to head comparison in the days taken for conversion is not possible because the only few conversion is performed in the pre interventional stage but for the majority of the patients in the stage 2 the conversion were made within 1–2 days (Table 3).

The costs of the antimicrobial agents are only taken in to the account because administered syringe had different cost with different brand. The cost of the antimicrobial agents used in the pre interventional period was found to be Rs.2, . The effect of the intervention were reflect in the reduction of overall consumption, especially in the use IV antimicrobial agents leads to reduce the post interventional phase cost to Rs 158356.182. The net differences in the antimicrobial treatment cost of the two study groups were found to be Rs . The mean average antimicrobial therapeutic cost for a patient in the pre interventional period was Rs 4519.50 but later in the post interventional period that was reduced to Rs 3167. A difference of Rs. 1352/patient were reduced in the cost of antibiotic treatment in the post interventional by the intervention. To compare the therapeutic cost of the different people in the selected population, the cost obtained in the groups were divided in to three categories such as cost below Rs 1000, more than Rs and in between them. Most of the patients in the pre-interventional period 71.16% (n = 37) and the rest of the patients are similarly distributed in the less than Rs. 1000 group 15.38% (n = 8), more than Rs. group. In the post interventional period the majority of the population is fall under the below Rs 1000 group and the rest of them are distributed under the class in which cost more than Rs. (n = 13), cost in between thousand and ten thousand (n = 7).

Antimicrobial agent utilization in reduced in the post interventional period, especially the parenteral antibiotics. In the initial phase of the study the consumption of the parenteral agents are more and that were reduced in the second phase. The patients who are discharged with parenteral antimicrobial agents are reduced between the two phases. The quantitative use of the parenteral AMA was found to be significantly reduced in the post-interventional phase in comparison to the pre-interventional phase (p = 0.028). The use of single parenteral AMA was reduced from 50.63% (n = 40) in the pre interventional period to 33.33% (n = 28) in the post-interventional phase. A similar reduction was also observed in use of four parenteral AMAs from 30.37% (N = 24) to 19.04% (n = 16). Because of the clinical condition for 18 patients two and three IV antibiotics were used in the post phase of the study, these number of antibiotics used only in 15 patients in the pre interventional phase.

The usage of antimicrobial agents also evaluated in terms of daily defined dose, 185 beds always occupied from total occupancy of 350 beds. Around 30 beds are always occupied with patients of general medicine departments. Thus the occupancy rate was found to be 16.21. The usage of parenteral antimicrobial agents was much higher in the post interventional group when compared to pre interventional group, 0.1413/100 bed days and 0.1603/100bed days. In contrast with the overall reduction in the parenteral usage, the DDD increment because of the utilization of parenteral antimicrobial agents usage in the post interventional period that were not used in the pre interventional period such as Cefuroxime, Ciprofloxacin, Levofloxacin, Metronidazole and Amoxicillin enzyme inhibitor combinations. Along with this the overall usage of antimicrobial agents were reduced from 1.2683 DDD/100bed days to 0.6953 DDD/100 bed days.

In the pre interventional observational period (pre ASP) no recommendations were performed. IV to per oral conversion guideline prepared and circulated, after that the clinical pharmacist made recommendations based on the same guideline to convert IV preparations to oral. The recommendations are performed to convert the intravenous parenteral antibiotic to oral agents in the patients who are satisfying the conversion criteria. Based on the clinical condition of the patient physician accepted and rejected the recommendations by the clinical pharmacist. In the post ASP three month period 39 recommendations were performed in the 36 patients those who are prescribed with IV parenteral antimicrobial agents, 14 patients had severe infection and need to continue the parenteral formulation. Physician accepted 36 recommendations out of 39 recommendations, the two recommendations rejected because the patients have suspected lung infections and fluid collections were observed in the chest x-ray. But all the 36 patients met the conversion criteria (Table 4).

Table 2
Usage of iv antibiotics pre and post intervention.

Parenteral Antibiotic	Population		Number Of IV Agetns	
	Before	After	Before	After
1	40	28	40 (50.63%)	28 (33.33%)
2	3	14	6 (7.5%)	28 (33.33%)
3	3	4	9(11.39%)	12(14.28%)
4	6	4	24(30.37%)	16 (19.04)
TOTAL	52	50	79	84

Table 3
Number of days taken for conversion and population.

Days taken for conversion	Intervention	
	Before	After
No Conversion	49 (94.23%)	15(30%)
Conversion after 1 day	1 (1.92%)	7 (14%)
Conversion after 2 days	0 (0%)	12 (24%)
Conversion after 3 days	0 (0%)	9 (18%)
Conversion after 4 days	0 (0%)	7 (14%)
Conversion after 5 days	2(3.84%)	0 (0%)

Table 4
Recommendattions and acceptance.

Recommendation	Number
PERFORMED	39 in 84 drugs (46.42%%)
ACCEPTED	36 (92.30%)
REJECTED	3 (8.33%)

4. Discussion

The study highlighted that, development of guidelines for the IV to PO conversion of AMAs in lines with the institutional antibiotic guidelines can significantly reduce the usage of parenteral therapy for unnecessary long durations and inappropriate circumstances. This can have positive impact on both the health and economic aspect from the patients' perspective.

The populations in the both period of the study were distributed in the all age groups and the distribution of the male and female characters are also similar. But when comparing the duration and the strength of the population, the current study is conducted for a 3 month with less than 50 patients per group and the other studies conducted for more than six months with more than 500 patients per group. Even if the sample size is adequate to find out the significance of the study, the sample size needs to be increased for the proper comparison with other studies. Because of the study focused in the cost minimization by the interventions the different indications is not taken into account.

The average duration of parenteral AMA therapy was reduced from 4 days to 2 days. The impact of the study can be observed from the fact that a 24% increase in the second day and 12.82% increase in the 1 day conversion were yielded as a result of the interventions executed. The patients in whom the conversion still took 4 or 5 days in the post-interventional period was due to the lack of anticipated clinical improvements after the 2 nd or 3 rd days of parenteral therapy. A checklist implemented interventional study by Dominik et al 36 in 2009 was supportive of the result obtained in the current study. The similar before after study conducted by Sevinc et al 18 Vogtländer et al 38 found their reduction in the days taken for conversion ranging from 6 to 4(days) is more than the current study and the study by McLaughlin et al 39 have the comparable date taken for conversion, 2–3 days. One of the pharmacist intervened study conducted in USA by Przybylski et al 40 were found to be a better therapy with few days(1.53) taken for conversion. The rate of conversion should be accessed in the conversion study to find the efficacy of the interventions and the recommendations. 39 conversions were made by the clinical pharmacist in the post interventional period from in 36 patients, 7 recommendations are rejected and the rest of them are ineligible for conversion. The 33.146% (118) conversions made by the Zeina M Shrayteh et al in 356 patients is not comparable to the significance of the current study recommendations impact, because the 42.85% (36) of the interventions were accepted by the physician and the conversion were made in 36 patient in the post interventional study period. Similar study conducted in the general medicine south Indian patients by Palaniswami A et al 41 were found to be conversion were made 28.57% of the population (n = 36) out of 126 patients with the effective interventions.

Testsuya Fukuda et al 42 conducted a study of the contribution of antimicrobial stewardship programs towards the reduction in cost of therapy in the community hospital in Japan for six-month period in the post-ASP period. Their interventional study reduces the overall cost of antimicrobial therapy to 25.8% for one year time span were by the 3 month current study reduced the overall antimicrobial cost to 19.5% of the control population. When depicted in terms of monetary units, INR ($1178.08) was saved in comparison to the pre-interventional phase which had placed a hefty economic burden on the patients. One year pharmacoeconomic impact measurement study by Przybylski et al 40 in the IV to oral conversion by the pharmacist a US hospital were reduced the cost $15149.24 while the one year current study made 7% ($1178.08) reduction in the treatment within 3 month span of time. Sequential interventional study by F.Al-Eidan et al 37 found that the cost of the antimicrobial agents reduced from Rs 1743 ($10.3) to Rs 670.20 ($26), a mean difference of Rs. 1000 per patient, by the preparation of the guideline and the recommendations by clinical pharmacist made the reduction in the antimicrobial cost to Rs. 1352/patient.

A study on recommendation based conversion of IV broad spectrum antimicrobial agents to its oral forms conducted by Przybylski KG et al 40 stimulated 52% reduction in parenteral AMA use and the impact of intervention in the current study much higher than the later study, 28.63% of the population absolute reduction is achieved. When comparing the consumption in standard terms such a daily defined dose, a 12 month interventional study by Dominik et al 36 was found to be by their conversion guideline and recommendation the usage was decreased by 27.2DDD/100 Bed days. For the current study the reduction of 0.010076 DDD/100 Bed days compared to the pre interventional period, indicating that 0.010076% of the population gets treatment daily. The difference in the fractional value of DDD/100 bed days in the current result because of the occupancy rate taken in percentage value instead of value 0 to 1.

Recommendations in the Japanese population by the Testsuya Fukuda et al 42 study 54% (251) were accepted, while comparing to the non-interventional group of the current study the clinical pharmacist recommendations to change the IV agents to oral formulations the 42.85% were accepted by the physician out of 39 recommendations made in 50 patients.

5. Recommendations and limitations of the study

The study will provide an idea regarding the conduction of the IV to oral programmed in the health care settings. The factors and the methodologies adopted was clearly explained the process of the study. These programme can be taken in to a long term basis to reduce the global outcome of the antimicrobial stewardship programme ie. Antimicrobial resistance. The limitations of the study were in the various aspects; the duration of the study is limited to 3 months and is not enough to get the correct outcome of the implemented guideline. The factors taken in the study is not covered all aspects of the antibiotics such as indication wise distribution and the different. Because of the cost minimization aspects only concentrated in the monetary outcome of the patient instead of other parameters.

6. Conclusion

This cost minimization study is properly executed without any difference in the outcome of the patients. After conversion to the oral formulation of the IV antibiotic none of the patient had any deleterious effect indicating that the outcome of the study is altered. Only the benefit to the patient is improved in terms of monetary value as well as the non −monetary measures. The reduction overall cost of the individual patient antibiotic treatment were achieved by the proper guideline implementation and recommendations. Timely conversions of intravenous to the oral route for antimicrobial agents are quintessential in maintaining patient safety and compliance. The same was implemented in the study site when all the parameters were estimated to be satisfactory for conversions. No undesirable effects were noticed in any of the patients after the conversions. The increase in the conversion rate clearly implicates the acceptance of guideline among the physicians of General Medicine department. The recommendations were successful in reducing both the length of stay and duration of parenteral therapy, therein reducing the consumption and cost of antimicrobial therapy. Such interventions have the potential to improve patient adherence to the regimen through reduced chances of injection associated discomfort and other adverse events to the patients in comparison to those on oral agents. The effect produced by the current study was equivalent to

those observed in similar studies conducted across the globe thus underlining the impact of Antimicrobial Stewardship Programme.

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