Empiric Treatment of Foot Infection in Patients with Severe Diabetes

Alexandre Sacchetti Bezerra1,2*, Flávia Altheman Loureiro2, Carla Maria Pasquareli Vázquez1, Afonso César Polimanti2 and Rafi Felício Bauab Dauar1

1Instituto de Infectologia Emilio Ribas, Brazil
2Faculdade de Medicina do ABC, Santo André, Brazil

ARTICLE INFO

Article history:
Received: 22 September, 2021
Accepted: 25 November, 2021
Published: 8 December, 2021

Keywords:
Foot infection
diabetes
diabetic patients
cultures
antibiotics

ABSTRACT

Background: Despite being treated with antibiotics of broad spectrum recommended by International Consensus, severe diabetic patients with lower limb infection do not present a positive clinical evolution during empirical treatment. This study’s bacterial profile was analysed and compared with other worldwide hospital centers.

Objective: To confirm the need of an individualized empirical treatment for severe diabetic patients with foot infection.

Methods: Retrospective analysis of cultures and antibiograms of severe diabetic patients admitted by foot infection.

Results: The results were consistent with the socioeconomic realities of developing countries. Gram-negative bacteria (52.11%) were present in most bone cultures. Results presented a high incidence of Enterococcus faecalis in both gram-positive (21.2%) and polymicrobial (34.7%) samples. Bacterial resistance with the use of ordinary antibiotics in the statistical analysis was high.

Conclusion: The community infections should undergo broad spectrum empirical therapy combining amikacin (80.43%) or meropenem (72.00%) with gram-negative and vancomycin (100%) or teicoplanin (90.00%) or linezolid (74.19%) with gram-positive.

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Introduction

Diabetes Mellitus (DM) is a chronic disease that has been growing rapidly worldwide. It is believed that there will be more than 550 million people with DM by 2030 [1-3]. It is widely known for many years that this population needs a specific multidisciplinary approach in order to control glycemic, neurological and infectious parameters, among others [4, 5]. The inefficient therapy approach gets worse morbidity and mortality dramatically. Per year, more than one million lower limb amputation are performed due to complications related to this disease [1, 4].

In 1996, the International Working Group on Diabetic Foot (IWGDF) was created and published its first International Consensus in 1999 [1, 2, 6]. Since then, the methodology for collecting and performing culture and antibiogram as well as therapeutic antibiotics use became part of the published Consensus [6-10]. Despite of the meticulous rigor, an empirical antibiotic therapy currently recommended in the guidelines of the American Society of Infectious Diseases (IDSA) for the treatment of severe diabetic patients does not present satisfactory clinical results. It is important to emphasize that these negative results refer only to empirical therapy, in other words, to treatment performed until individualized treatment based on the culture is possible.

Objective

The objective of the present study is to corroborate the need of an individualized empirical treatment for severe diabetic patients with foot infection in developing countries and to identify the antibiotics that should be used in our health service.
Methods

Retrospective study of bone cultures and antibiograms of severe diabetic patients admitted to the Centro Hospitalar Municipal Universitário de Santo André (Faculdade de Medicina do ABC) in 2018 by foot infection and therapeutic surgery. Patients come from a single community managed by a single integrated health system. As recommended in the 2012 and 2019 Consensus (IWGDF / IDS), in this studies, serious infection are considered the ones that occur in patients with metabolic changes or with signs of systemic toxicity. In the presence of critical lower limb ischaemia, any infection is considered severe and the patient must be hospitalized [1, 2, 6, 9]. The collected data was analyse according to the international CLSI protocol, following the standards and norms assumed by ANVISA NBR ISO/IEC 17025 (Collegiate Board Resolution - RDC 302, of October 13, 2005). Therefore, it is evident that no swab sample was considered, and all intra operative bone biopsies were done under appropriate conditions [6, 7, 11].

Statistical Analysis

The analyses were performed using the programme IBM SPSS Statistics version. The characterization of cultures and antibiograms was presented as percentage and frequency. The Binomial test compared the percentages of the number of cultures and the number of bacteria between gram-positive, gram-negative and both simultaneously. When the test presented significance between the results of antibiotics, the percentages of the results in each bacterium were compared (Table 1). The level of significance used was 5%.

Table 1: Number of the cultures and bacteria.

| Bacteria                              | Number of cultures | Number of bacteria |
|---------------------------------------|--------------------|--------------------|
|                                       | n                  | %                  | n                  | %                  |
| Gram-positive                         | 24a                | 33,80              | 33a                | 30,84              |
| Gram-negative                         | 37b                | 52,11              | 51b                | 47,66              |
| Gram-positive and Gram-negative       | 10c                | 14,08              | 23c                | 21,50              |

P-value*  

| a x b                                  | 0,100              | 0,049              |
| a x c                                  | 0,015              | 0,183              |
| b x c                                  | < 0,001            | 0,001              |

(*) Poisson test (statistically significant if p < 0,05).

Results

Among the 129 severe diabetic patients operated in 2018, 100 patients were included in this sample and 118 bone cultures were collected. Unfortunately, the data reported in medical records did not present albumin excretion rate (macroalbuminuria and microalbuminuria), patient weight, circumference waist measurement and glycosylated haemoglobin at the time of admission.

The linear analysis of the data presents a majority of males diagnosed with recent diabetes (Table 2). There was no growth of bacteria in 47 cultures (negative cultures) and there was growth in 71 cultures (positive cultures). A total of 107 bacteria were isolated. Among the 118 bone cultures, there was growth of only gram-positive bacteria in 24 cultures with 33 isolated bacteria, with the highest incidence being Staphylococcus aureus (27,2%) and Enterococcus faecalis (21,2%). There was a growth of only gram-negative bacteria in 37 cultures with 51 isolated bacteria, where Pseudomonas aeruginosa (13,7 %), Proteus mirabilis (117%), Escherichia coli (11,6%) and Morganella morganii (9,8%) had the highest incidence.

Table 2: Sample clinical characteristics.

| Clinical characteristics              | Percentage of patients |
|---------------------------------------|------------------------|
| Age 18-44                             | 23                     |
| Age 45-64                             | 52                     |
| Age > 64                              | 25                     |
| Patients who take aspirin             | 21                     |
| Patients who take statins             | 38                     |
| White patients not hispanics          | 54                     |
| Black patients not hispanics          | 38                     |
| Hispanics                             | 7                      |
| Other                                 | 1                      |
| Male gender                           | 62                     |
| Diagnosis of diabetes                 |                        |
| < 01 year                             | 42                     |
| 1-2 years                             | 31                     |
| >2 years                              | 27                     |
| Patients who take dapagliflozin       | 1                      |
| Patients who take metformin           | 42                     |
| Patients who take insulin             | 31                     |
In 10 cultures there was growth of both gram-positive and gram-negative bacteria with a total of 23 isolated bacteria, where *Enterococcus faecalis* (34.7%) and *Pseudomonas aeruginosa* (17.3%) had the highest incidence. The number of cultures presented statistical significance among bacteria, where gram-positive (33.80%) obtained a percentage similar to gram-negative (52.11%) and both were higher in percentage than the gram-positive and negative (14.08%). In addition, (Table 1) presents that the number of bacteria was also significant, gram-negative had the highest percentage (47.66%) compared to gram-positive (30.84%) and both simultaneously (21.50%). Table 3 illustrates that there was a significant difference between the results of sensitivity and resistance of gram-negative bacteria to some antibiotics.

### Table 3: Characterization and comparison of the gram-negative bacteria and antibiotics.

| Antibiotics                     | Results  | N   | %    | P-value* |
|---------------------------------|----------|-----|------|----------|
| Ampicillin                      | Resistant | 28  | 93.33| < 0.001  |
|                                 | Sensitive | 2   | 6.67 |          |
| Ampicillin/Sulbactam            | Resistant | 23  | 76.67| 0.005    |
|                                 | Sensitive | 7   | 23.33|          |
| Amikacin                        | Resistant | 9   | 19.57| < 0.001  |
|                                 | Sensitive | 37  | 80.43|          |
| Amoxicillin/Clavulanic acid     | Resistant | 22  | 68.75| 0.051    |
|                                 | Sensitive | 10  | 31.25|          |
| Aztreonam                       | Resistant | 34  | 87.18| < 0.001  |
|                                 | Sensitive | 5   | 12.82|          |
| Cefazolin                       | Resistant | 7   | 70.00| 0.344    |
|                                 | Sensitive | 3   | 30.00|          |
| Cefotaxime                      | Resistant | 15  | 88.24| 0.002    |
|                                 | Sensitive | 2   | 11.76|          |
| Cefoxitin                       | Resistant | 16  | 48.48| 0.999    |
|                                 | Sensitive | 17  | 51.52|          |
| Cefuroxime                      | Resistant | 15  | 93.75| 0.001    |
|                                 | Sensitive | 1   | 6.25 |          |
| Ceftazidime                     | Resistant | 39  | 78.00| < 0.001  |
|                                 | Sensitive | 11  | 22.00|          |
| Cefepime                        | Resistant | 37  | 75.51| < 0.001  |
|                                 | Sensitive | 12  | 24.49|          |
| Ceftriaxone                     | Resistant | 11  | 68.75| 0.210    |
|                                 | Sensitive | 5   | 31.25|          |
| Ciprofloxacin                   | Resistant | 32  | 65.31| 0.044    |
|                                 | Sensitive | 17  | 34.69|          |
| Colistin                        | Resistant | 6   | 54.55| 0.999    |
|                                 | Sensitive | 5   | 45.45|          |
| Ertapenem                       | Resistant | 12  | 30.77| 0.024    |
|                                 | Sensitive | 27  | 69.23|          |
| Fosfomycin                      | Resistant | 6   | 100.00| 0.031    |
|                                 | Sensitive | 0   | 0.00 |          |
| Gentamicin                      | Resistant | 24  | 48.98| 0.999    |
|                                 | Sensitive | 25  | 51.02|          |
| Imipenem                        | Resistant | 14  | 32.56| 0.032    |
|                                 | Sensitive | 29  | 67.44|          |
Levofloxacin  
Resistant 24 68.57 0.041
Sensitive 11 31.43

Meropenem  
Resistant 14 28.00 0.003
Sensitive 36 72.00

Piperacillin/tazobactam  
Resistant 21 45.65 0.659
Sensitive 25 54.35

Polymyxin B  
Resistant 2 16.67 0.039
Sensitive 10 83.33

Trimethoprim/sulfamethoxazole  
Resistant 24 72.73 0.014
Sensitive 9 27.27

Sulfazotrim  
Resistant 7 43.75 0.804
Sensitive 9 56.25

Tetracycline  
Resistant 7 100.00 0.016
Sensitive 0 0.00

Tobramycin  
Resistant 17 51.52 0.999
Sensitive 16 48.48

Tigecycline  
Resistant 7 53.85 0.999
Sensitive 6 46.15

Ticarcillin/clavulanic acid  
Resistant 5 62.50 0.727
Sensitive 3 37.50

(*) Binomial test (statistically significant if p < 0.05).

Gram-negative bacteria presented high resistance to cefepime (75.51%), ceftriaxone (68.75%), levofloxacin (68.57%) and ciprofloxacin (65.31%). They were sensitive to polymyxin B (83.33%), amikacin (80.43%), meropenem (72.00%), ertapenem (69.23%) and imipenem (67.44%). The analyse presented in (Table 3), that presented significance, were studied in (Table 4) in order to measure resistant gram-negative bacteria.

Table 4: Characterization and comparison of the gram-negative bacteria individual’s results.

| Bacteria                                      | Resistant | Sensitive | P value* |
|-----------------------------------------------|-----------|-----------|----------|
| Acinetobacter baumannii/haemolyticus          | 41        | 13        | < 0.001  |
| Burkholderia P. cepacia                       | 4         | 4         | 0.273    |
| Citrobacter freundii                          | 6         | 11        | 0.094    |
| E. coli                                       | 47        | 29        | 0.049    |
| Enterobacter cloacae                          | 15        | 7         | 0.041    |
| Klebsiella pneumoniae                         | 60        | 10        | < 0.001  |
| Morganella morganii                           | 30        | 25        | 0.590    |
| Proteus mirabilis                             | 32        | 40        | 0.410    |
| Proteus sp                                    | 5         | 3         | 0.219    |
| Proteus vulgaris                              | 22        | 19        | 0.755    |
| Providencia stuartii                          | 4         | 5         | 0.245    |
| Pseudomonas aeruginosa                        | 56        | 30        | 0.007    |
| Serratia marcescens                           | 7         | 11        | 0.121    |
| Serratia marcescens (First sample)            | 3         | 5         | 0.219    |
| Serratia marcescens (Second sample)           | 3         | 4         | 0.273    |

(*) Binomial test (statistically significant if p < 0.05).

Klebsiella pneumoniae (85.71%), Acinetobacter baumannii/haemolyticus (75.93%), Enterobacter cloacae (68.18%), Pseudomonas aeruginosa (65.12%) and E. coli (61.84%) were the bacteria with highest resistance to the tested antibiotics. Table 5 demonstrates that there was a significant difference between the results of sensitivity and resistance of gram-positive bacteria to some antibiotics. Gram-positive bacteria showed high resistance to ceftriaxone (78.95%), erythromycin (77.42%) and amoxicillin + clavulanic acid (76.47%). They were sensitive to daptomycin (100.00%), vancomycin (100.00%), teicoplanin (90.00%) and linezolid (74.19%). The analyse presented in (Table 5), that showed significance, was studied in (Table 6) in order to measure resistant gram-positive bacteria. Staphylococcus lugdunensis (100.00%), Streptococcus agalactiae (Group B) (100.00%), Streptococcus pyogenes (100.00%) and Enterococcus faecalis (76.47%) were the gram-positive bacteria with the greatest sensitivity to the tested antibiotics.
Table 5: Characterization and comparison of the gram-positive bacteria and antibiotics.

| Antibiotics                        | Results  | N   | %     | P-value* |
|------------------------------------|----------|-----|-------|----------|
| Ampicillin                         | Resistant | 16  | 59.26 | 0.442    |
|                                    | Sensitive | 11  | 40.74 |          |
| Ampicillin/Sulbactam               | Resistant | 12  | 70.59 | 0.143    |
|                                    | Sensitive | 5   | 29.41 |          |
| Amoxicillin/Clavulanic acid        | Resistant | 13  | 76.47 | 0.049    |
|                                    | Sensitive | 4   | 23.53 |          |
| Cefoxitin                          | Resistant | 0   | 0.00  | 0.250    |
|                                    | Sensitive | 3   | 100.00|          |
| Ceftriaxone                        | Resistant | 15  | 78.95 | 0.019    |
|                                    | Sensitive | 4   | 21.05 |          |
| Ciprofloxacin                      | Resistant | 13  | 43.33 | 0.585    |
|                                    | Sensitive | 17  | 56.67 |          |
| Clindamycin                        | Resistant | 15  | 60.00 | 0.424    |
|                                    | Sensitive | 10  | 40.00 |          |
| Daptomycin                         | Resistant | 0   | 0.00  | < 0.001  |
|                                    | Sensitive | 22  | 100.00|          |
| Erythromycin                       | Resistant | 24  | 77.42 | 0.003    |
|                                    | Sensitive | 7   | 22.58 |          |
| Streptomycin                       | Resistant | 3   | 100.00| 0.250    |
|                                    | Sensitive | 0   | 0.00  |          |
| Streptomycin of high-level         | Resistant | 2   | 28.57 | 0.453    |
|                                    | Sensitive | 5   | 71.43 |          |
| Gentamicin                         | Resistant | 12  | 48.00 | 0.999    |
|                                    | Sensitive | 13  | 52.00 |          |
| Gentamicin of high-level           | Resistant | 1   | 14.29 | 0.125    |
|                                    | Sensitive | 6   | 85.71 |          |
| Levofloxacin                       | Resistant | 12  | 40.00 | 0.362    |
|                                    | Sensitive | 18  | 60.00 |          |
| Linezolid                          | Resistant | 8   | 25.81 | 0.011    |
|                                    | Sensitive | 23  | 74.19 |          |
| Nitrofurantoin                     | Resistant | 2   | 33.33 | 0.688    |
|                                    | Sensitive | 4   | 66.67 |          |
| Norfloxacin                        | Resistant | 2   | 33.33 | 0.688    |
|                                    | Sensitive | 4   | 66.67 |          |
| Oxacillin                          | Resistant | 12  | 70.59 | 0.143    |
|                                    | Sensitive | 5   | 29.41 |          |
| Penicillin                         | Resistant | 19  | 57.58 | 0.487    |
|                                    | Sensitive | 14  | 42.42 |          |
| Rifampicin                         | Resistant | 7   | 29.17 | 0.064    |
|                                    | Sensitive | 17  | 70.83 |          |
| Sulfamethoxazole-trimethoprim      | Resistant | 7   | 36.84 | 0.359    |
|                                    | Sensitive | 12  | 63.16 |          |
| Sulfazotrim                        | Resistant | 2   | 66.67 | 0.999    |
|                                    | Sensitive | 1   | 33.33 |          |
| Synercid                           | Resistant | 10  | 38.46 | 0.327    |
|                                    | Sensitive | 16  | 61.54 |          |
| Tetracycline                       | Resistant | 12  | 37.50 | 0.215    |
|                                    | Sensitive | 20  | 62.50 |          |
| Teicoplanin                        | Resistant | 3   | 10.00 | < 0.001  |
|                                    | Sensitive | 27  | 90.00 |          |
| Vancomycin                         | Resistant | 0   | 0.00  | < 0.001  |
|                                    | Sensitive | 33  | 100.00|          |

(*) Binomial test (statistically significant if p < 0.05).
allows a more efficient, broad, definitive and less morbid therapeutic approach was followed by this study. In a study of 819 patients, Chen and contributors showed that clinical treatment without a surgical approach promotes slow healing of ulcers with a predisposition to worsening morbidity and mortality. Johani and collaborators recommended performing a surgical procedure after analysing a sample of 20 patients in which 80% had changes in bacterial biofilm [15-17].

In addition to the peculiar spectrum discussed above, the relation between sensitivity and resistance to antibiotics is particularly important. The sample of gram-negative has alarming resistance rates that includes ciprofloxacin (p = 0.04), amoxicillin (68.75%) and other drugs recommended by international Consensus. Similarly, gram-positive bacteria also exhibit atypical behaviour with high resistance to recommended antibiotics such as clindamycin (60%) [1, 3, 6]. For many decades, the Consensuses have recommended broad-spectrum empirical therapy such as ciprofloxacin associated with clindamycin or ceftriaxone together with clindamycin, among others. In 1986, Wheat and collaborators documented this in a two-year prospective study of 54 patients. Unfortunately, the broad spectrum coverage suggested earlier do not cover some hospital centers with a profile similar to Brazilian hospital centers [6, 14, 18].

Currently, it is possible to observe a change in the patterns found in cultures and antibiograms. Like this study, numerous academic groups suggest that empirical therapy should accompany these changes and be modified. Although they seem paradoxical, these considerations are not contradictory since they refer to vastly different institutions with different patients. While Young and contributors do not recommend treating empirically Pseudomonas sp., Ramakant and contributors request that the empirical antimicrobial therapy policy in tertiary level care be changed [4, 14, 19].

Within this apparent antagonism, many hospitals already use markers such as Procalcitonin (PCT) associated with Erythrocyte Sedimentation Rate (ESR) and C-reactive protein (CRP) curves in an attempt to make possible discoveries. Despite of the need of further studies, it is believed that the PCT composed of 116 amino acids, in addition to stratifying soft tissue infections from true osteomyelitis, can help to differentiate patients with infection from the sick without infection or even

Table 6: Characterization and comparison of the gram-positive bacteria individual’s results.

| Bacteria                      | Resistant n | Sensitive n | P value* |
|-------------------------------|-------------|-------------|----------|
| *Enterococcus avium*          | 4           | 11          | 0.118    |
| *Enterococcus faecalis*       | 8           | 26          | 0.003    |
| *Staphylococcus aureus*       | 24          | 35          | 0.193    |
| *Staphylococcus auricularis*  | 3           | 4           | 0.999    |
| *Staphylococcus epidermidis*  | 6           | 8           | 0.791    |
| *Staphylococcus hyicus*       | 4           | 2           | 0.688    |
| *Staphylococcus lugdunensis*  | 0           | 7           | 0.016    |
| *Staphylococcus sciuri*       | 8           | 11          | 0.648    |
| *Staphylococcus spp*          | 1           | 2           | 0.999    |
| *Staphylococcus spp coagulase negative* | 2    | 2           | 0.999    |
| *Staphylococcus xylosus*      | 3           | 3           | 0.999    |
| *Streptococcus agalactiae (Group B)* | 0   | 6           | 0.031    |
| *Streptococcus pyogenes*      | 0           | 3           | 0.031    |

(*) Binomial test (statistically significant if p < 0.05).

Discussion

Despite of the number of cultures presenting significance between different types of bacteria with a similar percentage between gram-positive and gram-negative bacteria as presented in (Table 1); this study differs from the literature, with higher incidence of gram-negative bacteria. Hatipoglu and contributors found, in a sample of 2,097 patients, a higher percentage of positives. The socioeconomic discrepancy that is exemplified in the incidence of Staphylococcus aureus (21.2%) and with cultures of gram-positive bacteria and in polymicrobial (34.7%) [12, 13].

In (Table 1), despite of the differences already explained, the results showed a reduced expression of polymicrobial and anaerobic cultures. Only 10 (14.08%) cultures had gram-positive and gram-negative bacteria. Unlike this study, Ramakant and contributors published a retrospective study involving 447 hospitalized patients with a majority of 66% polymicrobials. Zubair and colleagues found 31.4% of anaerobes in their study. The unmonitored use of antibiotics in an extra-hospital environment prior to hospitalization, as well as repeated hospitalizations in different medical services without standardization between hospitals may justify this differences [13, 14].

Our sample presents the peculiarity of 39.83% of negative cultures, in other words, without the growth of bacteria. This peculiarity relates to the fact that all procedures were performed by vascular surgeons in an operating room under general anaesthesia or spinal sympathetic block. None of the collected fragments were acquired under local anaesthesia or simple sedation by nurses or doctors of another specialty. The guidelines of the literature in which the effective surgical procedure

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|-------------------------------|-------------|-------------|----------|
| *Enterococcus avium*          | 4           | 11          | 0.118    |
| *Enterococcus faecalis*       | 8           | 26          | 0.003    |
| *Staphylococcus aureus*       | 24          | 35          | 0.193    |
| *Staphylococcus auricularis*  | 3           | 4           | 0.999    |
| *Staphylococcus epidermidis*  | 6           | 8           | 0.791    |
| *Staphylococcus hyicus*       | 4           | 2           | 0.688    |
| *Staphylococcus lugdunensis*  | 0           | 7           | 0.016    |
| *Staphylococcus sciuri*       | 8           | 11          | 0.648    |
| *Staphylococcus spp*          | 1           | 2           | 0.999    |
| *Staphylococcus spp coagulase negative* | 2    | 2           | 0.999    |
| *Staphylococcus xylosus*      | 3           | 3           | 0.999    |
| *Streptococcus agalactiae (Group B)* | 0   | 6           | 0.031    |
| *Streptococcus pyogenes*      | 0           | 3           | 0.031    |

(*) Binomial test (statistically significant if p < 0.05).
distinguish between sepsis and local infections. Like ESR and CRP, PCT can also denote and guide possible therapeutic success with the reduction of its serum curve [20, 21]. In the future, there will probably be serum markers that, in addition to being predictive of prognosis, will help in the empirical therapy of severe diabetic patients.

Conclusion

The recommendation of broad-spectrum antibiotic therapy with drugs used in multidrug-resistant bacteria for all patients with severe infection regardless of their origin, comorbidities or previous use of antibiotics can trigger the abuse of antibiotics that goes global policies to reduce antimicrobial resistance but in severe diabetic patients with gram-negative bacteria flora present better results if treated empirically with amikacin (80.43%) or meropenem (72.00%), after the mandatory assessment of the clinical condition of each patient using parameters such as creatinine clearance among many others. Similarly, the flora of gram-positive bacteria should receive vancomycin (100.00%) or teicoplanin (90.00%) or linezolid (74.19%) until individualized treatment based on the antibiograms is possible.

Conflicts of Interest

None.

Author Contributions

Alexandre Sacchetti Bezerra: Substantial contributions to the conception or design of the work, or the acquisition, analysis, or interpretation of data for the work, drafting the work or revising it critically for important intellectual content; Rafi Felicio Bauab Dauar: Substantial contributions to the conception or design of the work, or the acquisition, analysis or interpretation of data for the work; Carla Maria Pasquareli Vázquez: Final approval of the version to be published.

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