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Antihelminthic resistance, who is to be blamed; the host, the parasite or the drug: A review.

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Abstract

Antihelminthic resistance encountered in the treatment and control of parasitic infections has been of great concern for human and veterinary tropical medicine. This study became necessary to critically analyze the major causes of antihelminthic resistance and how to address them. Many parasitic helminthes of veterinary importance have genetic features that confer antihelminthic resistance. This of course is becoming a worldwide constraint in animal production. The development of antihelminthic resistance poses a great threat to future productivity and general wellbeing of the animals. Development of variable degrees of resistance among different familiesof helminthes have been reported for all the major groups of antihelminthic parasites, their hosts and of course the drugs used in combating them. It has also been observed that frequent usage of the same group of antihelminthics, usage in incorrect proportions, prophylactic mass treatment of animals, helminthes species, parasite strain among others have contributed to the widespread development of antihelminthic resistance. The extent of this problem with regard to drug, host and parasite resistance in veterinary medicine is likely to increase. This review is focused on answering the pertinent question of who takes the blame (the host, parasite or drug) in antihelminthic resistance with a view to contributing to the existing key points aiding the control or at least reducing the occurrence of resistance.

Keywords: *Antihelminthic, Resistance, Host, Parasite, Drug, Control.*

Résistance aux antihelminthiques : qui est à blâmer ; l'hôte, le parasite ou le médicament : une revue

Résumé

La résistance aux antihelminthiques rencontrée dans le traitement et le contrôle des infections parasitaires est une préoccupation majeure en médecine tropicale humaine et vétérinaire. Cette étude s'avère nécessaire pour analyser de manière critique les causes principales de la résistance aux antihelminthiques et les moyens d'y remédier. De nombreux helminthes parasites d'importance vétérinaire possèdent des caractéristiques génétiques qui confèrent une résistance aux antihelminthiques. Cela devient bien sûr une contrainte mondiale pour la production animale. Le développement de la résistance aux antihelminthiques constitue une grave menace pour la productivité future et le bien-être général des animaux. Le développement de différents degrés de résistance parmi diverses familles d'helminthes a été rapporté pour tous les principaux groupes de parasites antihelminthiques, leurs hôtes et bien sûr les médicaments utilisés pour les combattre. Il a également été observé que l'utilisation fréquente du même groupe d'antihelminthiques, leur administration à des doses incorrectes, le traitement prophylactique de masse des animaux, les espèces

d'helminthes, les souches parasitaires, entre autres, ont contribué à l'émergence généralisée de la résistance aux antihelminthiques. L'ampleur de ce problème concernant la résistance du médicament, de l'hôte et du parasite en médecine vétérinaire est susceptible d'augmenter. Cette revue se concentre sur la réponse à la question pertinente de savoir qui endosse la responsabilité (l'hôte, le parasite ou le médicament) dans la résistance aux antihelminthiques, dans le but de contribuer aux points clés existants aidant au contrôle ou du moins à la réduction de l'occurrence de cette résistance.

***Mots-clés** : Antihelminthique, Résistance, Hôte, Parasite, Médicament, Contrôle.*

. مقاومة مضادات الديدان، من يُلام: العائل، أم الطفيلي، أم الدواء؟ مراجعة

مقاومة مضادات الديدان التي تواجه في علاج والسيطرة على العدوى الطفيلية أصبحت مصدر قلق كبير في الطب الاستوائي البشري والبيطري. وقد أصبحت هذه الدراسة ضرورية لتحليل الأسباب الرئيسية لمقاومة مضادات الديدان وكيفية معالجتها بشكل نقدي. تمتلك العديد من الديدان الطفيلية ذات الأهمية البيطرية خصائص جينية تمنحها مقاومة لمضادات الديدان، وهو ما يشكل عائقاً عالمياً متزايداً في إنتاج الحيوانات. إن تطور مقاومة مضادات الديدان يشكل تهديداً كبيراً للإنتاجية المستقبلية وللصحة العامة للحيوانات. لقد تم الإبلاغ عن تطور درجات متفاوتة من المقاومة بين العائلات المختلفة من الديدان الطفيلية تجاه جميع المجموعات الرئيسية من مضادات الديدان، وكذلك تجاه العائل (الحيوان) والأدوية المستخدمة في مكافحتها. كما لوحظ أن الاستخدام المتكرر لنفس مجموعة مضادات الديدان، والاستخدام بنسب غير صحيحة، والعلاج الجماعي الوقائي للحيوانات، ونوع الديدان، وسلالة الطفيليات، من بين عوامل أخرى، قد ساهمت في الانتشار الواسع لمقاومة مضادات الديدان. ومن المرجح أن تتفاقم هذه المشكلة فيما يتعلق بالمقاومة تجاه الأدوية والعائل والطفيلي في الطب البيطري. وتركز هذه المراجعة على محاولة الإجابة عن السؤال الجوهري: من يتحمل المسؤولية في مقاومة مضادات الديدان – هل هو العائل، أم الطفيلي، أم الدواء؟ – وذلك بهدف الإسهام في النقاط الأساسية القائمة التي تساعد في السيطرة على المقاومة أو على الأقل التقليل من حدوثها.

الكلمات المفتاحية: مضادات الديدان، المقاومة، العائل، الطفيلي، الدواء، السيطرة

Introduction

Helminthes are a group of parasitic worms that survive by feeding on living hosts to gain nourishment and often times resulting in infection or even death of their hosts. They encompass nematodes, cestodes and trematodes which constitute major health problems for both humans and animals in many countries of the world. (Kaplan 2004., Hotez *et al*; 2008). They are characterized by round, segmented or elongated bodies. They share similar morphology and are multicellular parasites that are visible to the naked eyes. They live in the intestine of their hosts invading other organs in the body, making their host to exhibit acute or chronic clinical symptoms and at most times cause death. Antihelminthic drugs on the other hand comprise of a group of antiparasitic drugs that expel parasitic worms (helminthes) and other internal parasites from the body either by stunning or killing them without causing significant damage to the host. Antihelminthic resistance occurs when a susceptible population shows a decrease in response to treatment or the maximum dose of drugs that can be tolerated by the host has no effect on the parasite (Coles *et al*; 2000). Antihelminthic resistance has become a global challenge which threatens the profitability of these animals (Besier, 2003). Although the impact of these helminthes could be reduced drastically by improved sanitation for humans, management practices designed to reduce the larval development and

pasture control in grazing animals.Over the years, these practices have yielded very little or no significant results. Various factors could contribute to the ability of parasites to survive doses of drugs that would normally kill parasites of that same specie and strain. This resistance could be inherited because the survivors of treatments pass genes for resistance to their offspring. Understanding the development of antihelminthic resistance by either the parasite, host or inadequate drug proportion is crucial to monitoring and eventual control of this problem. In order to provide solutions for the threats characterized by the lingering spread of this resistance especially in animals of veterinary importance, a number of urgent questions are yearning for answers. The question seeks for answers as to who takes the blame in antihelminthic resistance, the drug, host or parasite. Therefore within the scope of this study, various factors contributing to the development of this resistance will be considered thereby providing solutions or answers to this very important question which will in turn reduce or even drastically curb this helminthic resistance.

Previous studies suggest that effective control schemes should not only rely on the use of antihelminthics but include other practices like combination of drug strategy and strict quarantine measures. Studies of parasite resistant breeds, nutritional status of the host (animal), pasture management to reduce exposure to the parasite, reduction of larva development, antihelmithic vaccines and broad spectrum antihelminthics. These measures have been proven to be environmental friendly, coupled with a reduction of reliance on the use of chemicals.

Literature Review

In animals, resistance to anthelmintics occurs rapidly after their introduction. There has been considerable debate about the definition of resistance and tolerance which are used interchangeably to describe the relationship between success and failure of drug treatment. However, as stated by Coles (2000) resistance occurs when a susceptible population shows any decrease in response to treatment and is complete when the maximum dose of drug that can be tolerated by the host has no effect on the parasite. Unfortunately, the decline in response can manifest in different ways, either as a heritable decline in the efficacy of an anthelmintic against a population of parasites that is generally susceptible to that drug or as a decrease in the time a drug treatment exerts its effect, with resistant populations requiring more frequent treatments than previously administered. Pichard (2007), to provide a scientific basis for resistance has identified an increase in the proportion of organisms in a population carrying a gene demonstrated to be linked with resistance. He further stated that these heritable changes can be either genetic (including mutations, deletions or amplifications of specific genes) or epigenetic whereby methylation of genes or promoter regions of the genes change the gene expression in response to the drug.

Jackson and Coop (2002) observed that in animals, anthelmintic-resistant is already creating a serious problemin in veterinary practice. In Australia, for example, the prevalence and severity of resistance threatens the profitability of the entireindustry (Besier 2003) in a report stated that resistance has arisen to all of the major families of broad spectrum antihelmintics.Sangster and Gill (1999) also reported resistance tobenzimidazoles (BZ), levamisole (LEV) and the other nicotinic agents, in addition to the avermectins and milbemycins (AM) (including ivermectin, doramectin and moxidectin).

Helminthes that are resistant to other narrow spectrum antihelmintics such as closantel, have also been reported. Of greater concern is the spread of resistance to triclabendazole, the main drug used to treat fluke infections because of its high activity against the migrating immature stages. Resistance was first reported in Australia in 1995 by Overendand Bowen (1995) and has since been described in the Netherlands, UK and Ireland. At the same time, there has been a dramatic resurgence of fasciolosis because of climate change and the advent of milder, wetter weather as reported by Mitchel (2002).

Antihelmintic resistance is a threat to agricultural incomes and has been reported from all the four corners of the world to all available drugs, in all classes of helminthes (Lalchhandama, 2010).

The general consensus as reported by Silvestre and Humbert (2002) is that antihelmintic resistance appears to be a pre-adaptive heritable phenomenon with the gene or genes conferring resistance being present within the parasite population even prior to the drug being used for the first time. Under these circumstances resistance arises as a result of selection through exposure of the worm population to an antihelmintic. When an animal is optimally exposed to an antihelmintic, the only worms that should survive are those that carry the genes that confer resistance. For a short period (until the animal becomes re-infected with drug susceptible worms from pasture) the resistant survivors are the only worms laying eggs and in this way the gene pool for resistance is increased. The rate of development of resistance is influenced by many factors among which are frequency of treatment. It has been observed by Taylor and Hunt (2002) that frequent usage of the same group of anthelmintic may result in the development of anti helminthic resistance. There is also evidence that resistance develops more rapidly in regions where animals are worn regularly. Antihelmintic resistance in *haemonchus contortus* has been reported in some humid tropical areas where 10 to 15 treatments per year were used to control this parasite in small ruminants Coles (2010), however said that drug resistance can also be selected at lower treatment frequencies, especially when the same drug is used over many years. He also reported that the development of antihelminthicresistance also can occur even when only two or three treatments were given annually.

Underdosing is generally considered an important factor in the development of antihelminthic resistance because subtherapeutic doses might allow the survival of heterozygous resistant worms as reported by Smith (1990). Several laboratory experiments have shown that underdosing contributes to the selection of resistant or tolerant strains (Hoekstra and Visser, 1997). Moreover, variation in bioavailability in different host species also is crucial in making decision about correct dose. Some indirect field evidence further supported this conclusion. For example, the bioavailability of benzimidazole and levamisole is much lower in goats than in sheep, resultantly those goats should be treated with dosages 1.5 to 2 times higher (the single dose is much less inferior than “sub-optimal”, it is rather near half the dose necessary for goats) than those given to sheep (Hennessy, 1995) For many years, however, sheep and goats were given the same antihelmintic doses.

The fact that antihelminthic resistance is very frequent and widespread in goats may be a direct consequence of difference in metabolism of drugs. To reduce the costs of antihelmintic treatment in developing countries, the use of lower dosages than the recommended therapeutic ones has been advocated. Such practices should clearly

be avoided. Most of the currently applied antihelmintics are in fact subcurative in at least part of the population. Additionally, there are a few species of nematodes which are present as mixed infection in animals throughout the world which respond to different groups of antihelmintics differently due to the irregular susceptibility of these species to a given antihelmintic. Warren *et al*., (1993) noted that this can be considered acceptable for morbidity control, but in the long run such strategies may contribute to the development of resistance. It has also been reported that prophylactic mass treatments of domestic animals have contributed to the widespread development of antihelminthic resistance. Computer models indicate that the development of resistance is delayed when 20% of the flock is left untreated Van Wyk (2001), but it needs confirmation through experimentation. This approach would ensure that the progeny of the worms surviving treatment will not consist only of resistant worms. Leaving a part of the group untreated, especially the members carrying the lowest worm burdens should not necessarily reduce the overall impact of the treatment. In worm control in livestock, regular moving of the flocks to clean pastures after mass treatment and planning to administer treatment in the dry seasons is a common practice to reduce rapid reinfection. However, Taylor *et al*; (2002) and Smith (1990) reported that these actions result in the next helminth generation which consists almost completely of worms that survived therapy and therefore might contribute to the development of resistance.

Also frequent and continuous use of a single drug will definitely lead to the development of resistance. Pal and Qayyum (2001), cited an example of a single drug which is usually very effective in the first years and when it was continuously used, no longer worked. In a survey of sheep farmers in Tennessee, Reinemeyer *et al*., (1992) found that one out of every two flocks was dosed with a single antihelmintic until it failed. Long-term use of levamisole in cattle also led to the development of resistance, although the annual treatment frequency was low and cattle helminthes seemed to develop resistance less easily than do worms in small ruminants.Geerts *et al*;(1987) also reported that frequent use of ivermectin without alternation with other drugs is the reason for the fast development of resistance in *Haemonchus contortus* in South Africa and New Zealand and other countries of the world. From a clinical standpoint, it is important to appreciate that resistance is a genetic trait in parasites. Therefore, prevention of resistance must be aimed at reducing the rate with which resistance traits accumulate and strategies designed to slow the development of resistance must be deployed early in the process of resistance, before there could be any clinical evidence of reduced drug effect.

VanWyk in a study in 2001 observed that parasitologists now consider levels of resistance as the single most important factor contributing to selection for antihelmintic resistant parasite. Worms with resistance provide a pool of genes susceptible to anthelmintics, thus diluting the frequency of resistant genes. For many years, parasitologists and veterinarians have recommended that all animals be treated with an antihelmintic at the same time. However, this strategy has turned out to be unsustainable and parasitologists now favor a selective approach where only animals in need of treatment receive treatment. The appearance of avermectin resistance in *Telodorsagia* spp. in Western Australia after only two treatments with the drug illustrates the power of selection Sangster and Gill (1995).

Effective management strategies to prevent development of antihelmintic resistance are worthless if producers purchase resistant helminthes residing in breeding stock. Therefore, strict quarantine procedures should be instituted for all new additions. This practice is more important than ever, as in recent years several farms with high-quality breeding stock dispersed herds where *Heamonchus contortus* and *Taenia colubriformis* were resistant to benzimidazoles and moxidectin. There is no faster way to spread resistance than to bring gastrointestinal nematodes to a farm. The current recommendation is to quarantine (on dry lot where faeces can be removed) every new addition, dose with triple-class antihelmintic therapy and perform faecal egg count reduction tests. Feed should be withheld for 24 hours before treatment, then moxidectin, levamisole, and albendazole should be administered consecutively (do not mix drugs together) at the appropriate dose for sheep or goats. Fourteen days later, treated animals should be evaluated by faecal egg count and faecal floatation techniques. The faecal egg count should be zero and floatation should yield very few or no eggs. Furthermore, after receiving this treatment, animals should be placed on a contaminated pasture. Fleming *et al*., (2006) warned that never should an animal be placed onto a clean pasture after a triple antihelmintic class treatment regimen is administered, because any surviving worms will be tripple resistant and there will be no resistance on pasture to dilute the future transmission of any eggs that are shed.

Treating simultaneously with two drugs from different antihelmintic classes is one method of preventing the development of antihelmintic resistance. A computer based model has documented that if this strategy is used when the drugs are first introduced, before there is any selection for resistance to either drug, appreciable resistance will not develop for over twenty (20) years. However, once resistance is encountered in helminthe populations, this strategy will probably not be successful. Compared with individual drug effects, antihelmintics of different chemical classes administered together induce a synergistic effect, resulting in clinically relevant increases in the efficacy of treatment. This synergistic effect is most pronounced when the level of resistance is low. Once high-level resistance to both drugs is present, the synergistic effect is unlikely to produce acceptable levels of efficacy. Synergistic combinations have been described for both human and veterinary infections. For example, Utzingeret *et al*., (2004) reported that combinations of praziquantel with oxamniquine or artemether have been shown to be synergistic for the treatment of schistosome infections. He further stated that synergism between albendazole and ivermectin or diethylcarbamazine and between mebendazole and levamisole or pyrantel has been described for the treatment of soil-transmitted helminths. For veterinary parasites, Bennet *et al*., (1980) reported that a combination of mebendazole and levamisole has been shown to be synergistic against *Heamonchus contortus* in sheep. Hopkins (1991) also reported that infebantel and pyrantel against *Ancylostoma caninum* in dogs. Melillon *et al.,* (1994) reported the effectiveness of pyrantel against *Toxocara canis in vitro.* For the nematodes of small ruminants, Leathwick (2012) concluded that the use of combinations serve dual purposes of maintaining helminthes control in the presence of antihelminthic resistance sometimes involving more than one parasite species or more than one class of antihelmintic and delaying the development of resistance to the component chemical classes in those species in which resistance is not yet evident.

There is considerable evidence that part of the variation in resistance to helminths infection is under genetic control. Resistance is most likely based on inheritance of genes that play a principal role in expression of host immunity. Several breeds of sheep around the globe are known to be relatively resistant to infection. Using such breeds exclusively or in crossbreeding programs would certainly lead to improved resistance to worm infection, but some level of production might be sacrificed as suggested by Gasber (1999). Although such a strategy may be acceptable to some, selection for resistant animals within a breed also is a viable option. Within a breed, animals become more resistant to infection with age as their immune system become more competent to combat infection.

Coop (2001), observed that the strongest link between nutrition and parasitism has been illustrated between protein intake and resistance to gastro-intestinal parasites. The most dramatic has been the abolishment of the periparturient egg increase in lambing ewes by providing protein at 130% of requirements. Reducing exposure of susceptible hosts in control programs is paramount. The goal of pasture management is to provide safe pastures for grazing. A safe pasture is one that has not had sheep or goat grazed on it for 6 months during cool/cold weather or 3 months during hot or dry season. Berger (1999), reported that pasture management must include monitoring the condition of the herbage to ensure that overgrazing does not occur and to maintain a productive pasture. At the onset of the rainy season, reduced pasture contamination remains the most important aspect of control by engaging strategic deworming to remove arrested or recently emerged larvae before they contaminate the pasture. Again, two weeks treatment after a rain will definitely remove recently acquired worms before they can begin shedding eggs.

As a consequence of drug resistance, efforts have increased in recent years to develop functional vaccines. This has been made possible by newer technologies in gene discovery and antigen identification, characterization, and production. At present, only one worm vaccine is in the market for the cattle lung nematode *Dictyocaulus viviparous* (Bovilis Lung worm). The increasing drug resistance of gastrointestinal nematodes has renewed intense interest in developing vaccines for these important veterinary pathogens. This vaccine has been tested successfully only in sheep under experimental conditions and has had limited success under field conditions. The reasons for this lack of success are unclear.

In the last two decades, there has been a resurgence of interest in traditional health-care practices all over the world. These traditional practices involve diagnostics, herd grazing and pasture management as well as manipulation and treatment. The incidence of antihelminthic resistance has simply forced veterinarians/producers to adopt alternative control strategies. Plants have been used from ancient times to cure diseases of man and animals. Satyavati *et al*; (2000) revealed that the plant kingdom is known to provide a rich source of botanical antihelmintics. Several medicinal plants have been used to treat parasitic infections in man and animals. There are many plants which have been reported in the literature by many authors for their antihelmintic importance. Among the most common medicinal plants which have antihelmintic effect are *Allium sativum, Nigella sativa, Artemisia* spp., *Balanites aegyptiaca*, *Acacia* spp., cucurbile (pumpkin seeds), *Commiphoramolmol* (Myrrh), *Calendula micrantha officinalis, Peganum harmala* and

Tumeric (curcumina), Shalaby *et al*., (2012), Massoud *et al*., (2012).

Additionally, Neizen (1990) added that various pasture tanniferous plants have also been investigated for potential effect against either incoming parasite larvae or already established worms. These plants can be a promising future for the control of helminthes which had previously shown resistance to synthetic drugs.

Discussion

From the information gathered from literature, antihelminthic resistance is a global threat to the maximum productivity of animals. There is yet no substantial evidence that resistance to commonly used antihelmintics should be attributed to either the host (animal or human), parasite (helminthes) or the drug (antihelminthics). It has been observed that various factors have been contributory to this resistance, and they will be enumerated in this text as it relates to each of them.

1. The Host: The host (animal) play a very significant role in antihelminthic resistance based on their inheritance of gene that confer antihelminthic resistance mostly because of previous exposure. For example, some breeds of sheep have this resistant gene and that of course contributes to antihelminthic resistance in the face of infection. Also, cattle helminthes seem to develop resistance less easily than do those in small ruminants. Healthy adult (host) with good nutritional status (when the animal has high intake of protein) become resistant to helminthic infections due to their strong and competent immune system. Treatment of the host with low helminth burden does little to control the helminthes by removing the vital source of refugia thereby accelerating the evolution of resistance (Fojo 2007).

2. The Parasite: The parasite otherwise known as the helminth in this case can mimic the hosts' protein thereby becoming resistant to antihelminthics. This is possible especially when the immune system of the host is compromised. Irregular susceptibility of the parasite species to a given antihelminthic can encourage resistance. Example, there are some strain or developmental stages of the parasite that are not affected by certain antihelminthics, therefore the parasite remains resistant if treated with such. Also, free living stages of the parasite in the environment at the time of treatment also become resistant Sreter *et al.,* (1994).

3. The Drug: Most of the causes of antihelminthic resistance revolve around the drug factor. From studies of different authors, drug resistance in antihelminthic treatment has become worrisome in veterinary practice. The drug is basically the recommended remedy against helminthes infection but when it becomes resistant certainly calls for panic. But there are several factors which may confer resistance on the drug, example routine benzimidazoles, Ivermectin and Moxidectin have been used routinely over the years and the helminthes have developed resistance against them.

Most of the commonly used antihelmintics belong to one of three chemical classes, benzimidazoles, imidazothiazoles and macrocyclic lactones within which all individual compounds act in a similar fashion. Thus, resistance to one compound may be accompanied by resistance to other members of the group, Sangster and Gill (1999).

Again, the drug may be resistant if the composition with which it is made up and cannot combat the helminthe parasite for which it is administered. Plant extract has also been found to be cheaper, more effective in recent times and as an alternative treatment overcome resistance.

Recommendation

Indiscriminate mass treatment (without any previous screening of the population) should be applied only in areas and groups where the impact of helminths and the benefits expected outweigh the costs and burden on the health system. Single drug regime should be discouraged instead combination of two drugs from different antihelminthic classes should be used simultaneously which will produce synergistic effect. The frequency of treatments should be reduced preferably one per year and combined with other control measures to maximize its effect. Exposure of the whole parasite population to the drug should be avoided by timing period of treatment during low-transmission seasons. The correct dosage of antihelmintics should be used for morbidity control programmes. Counterfeit antihelmintics should be avoided by imposing adequate quality standards on wholesale suppliers for national health care systems and special control programs. Monitoring the development of antihelminthic resistance should be an obligatory part of large-scale worm control programs. Every exposure of a target parasite to an antihelmintic exerts some selection pressure for development of resistance. Therefore, management practices designed to reduce exposure to parasites and to minimize the frequency of antihelmintic use should be recommended. The development of an antihelmintic resistance problem may theoretically be delayed by rotating chemicals with different modes of action annually between dosing seasons. Drug combinations may be another appropriate choice, provided the antihelmintics used in the combination are both effective and selective for different resistance mechanisms. In parasite control, economic benefit is best obtained by careful management practices. Planned (or targeted) treatment of a whole flock or herd should be based on the biology, ecology and epidemiology of the parasites with particular reference to climatic conditions.

Conclusion

Antihelminthic resistance is a threatening problem to the livestock industry posing very serious challenge to the future welfare and animal production globally. The factors contributing to this resistance are very encompassing with very significant roles played by the "HOST, PARASITE AND DRUG. Therefore, none of these should be blamed instead recommended management practices and various measures enumerated in this review should be strictly adhered to. When adequate strategies are implemented, the development of resistance may be delayed or even curbed completely.

It's only then that the issue of antihelminthic resistance can be completely overcome.

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