NIGERIAN VETERINARY JOURNAL

ISSN 0331-3026

Nig. Vet. J., September 2017 **Vol 38 (3): 250-259.**

ORIGINAL ARTICLE

Drugs Prescription Pattern in Dogs Diagnosed with Parvovirus Enteritis in Some Veterinary Clinics in Nigeria

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SUMMARY

Canine parvovirus enteritis affects predominantly puppies with a high prevalence rate in Nigeria and is characterized by diarrhea, vomiting, anorexia and leucopenia. Treatment is non-specific; hence array of medications are usually prescribed to manage the condition symptomatically. Irrational drugs prescription has been reported to be one of the causes of therapeutic failures and adverse drug reactions in veterinary medicine. This study was therefore designed to evaluate the pattern of drugs prescription in dogs diagnosed with parvovirus enteritis in some small animal clinics in Nigeria. The study was carried out in 10 states of Nigeria and Abuja. A retrospective study of drugs prescription pattern in dogs diagnosed with CPE, including polypharmacy, prescription rates, and dose regimen of gentamicin in 20 veterinary clinics were conducted from January, 2010 to December, 2014. Results showed that 554 (80.6%) of 687 patients were administered ≥4 drugs per encounter. Of the 2,482 drugs prescribed at the different clinics, antibiotics had the highest prescription rate of 42.3% (1,050). Gentamicin was the most frequently prescribed antibiotic which accounted for 23.8% (250) prescription rate. However, 57.2% (143) of the patients were under-dosed (<6mg/kg). Also, non-essential prescription of non-steroidal anti-inflammatory and gastrointestinal modulating drugs, including ranitidine were observed. This study has demonstrated that most drug prescriptions for dogs with parvovirus enteritis in Nigeria are inappropriate. This could have contributed to poor therapeutic outcomes common in parvovirus enteritis management. Consequently, Veterinarians should be rational in drugs prescription in order to optimize therapeutic efficacy and minimize adverse drug effects.

Key words: Parvovirus enteritis, Prescription pattern, Gentamicin, Dog, Nigeria.

INTRODUCTION

Canine parvovirus enteritis (CPE) is a highly contagious disease affecting predominantly young dogs caused by canine parvovirus which is transmitted through direct or indirect contact with contaminated feces or fomites (Appel *et al*., 1979; Kahn, 2010). It is characterized by vomiting, diarrhea, lethargy, hypoglycemia and leucopenia (Streck *et al*., 2009). In spite of the prophylactic measures and various treatment

protocols described for CPE, its prevalence is still high in Nigeria (Shima *et al.*, 2015). Survival rates have been reported to be as high as 80-95% when managed early and aggressively, but as low as 9.1% in the absence of adequate management (Prittie, 20045; Goddard and Leisewitz, 2010). Currently, there is no specific treatment for this viral condition; however, good survival rate can be achieved with appropriate supportive and symptomatic management (Boothe, 2012). Consequently, management is tailored towards treating symptoms associated with the disease while the virus runs its course. This management involves prescription of an array of medications, in addition to supportive nutrition.

Irrational drug prescriptions by clinicians have been reported to be a common practice in most developing countries (Isenalumehe and Oviawe, 1988; Laing, 1990). Rational use of drugs requires that patients receive medications appropriate to their clinical needs, in doses that meet their individual requirements for an adequate period of time and at the lowest cost to the client (WHO, 1993). This has been reported to reduce therapeutic failures, cost of treatment and adverse effects (Pramil, 2012). Thus, increased awareness of rational drugs prescription is essential to minimize adverse effects and optimize therapeutic outcomes. There is paucity of information on the prescription pattern of drugs in small animal practice in Nigeria. The objective of this study was to evaluate the pattern of drugs prescription in dogs diagnosed with CPE in some small animal clinics in Nigeria.

MATERIALS AND METHODS

Study Locations

This study was conducted in 10 states and Abuja (Federal Capital Territory). The inclusion criterion for each study location was based on high level of small animal practice. A total of 20 small animal clinics were included in this study comprising of 7 state owned veterinary clinics, 10 private veterinary clinics and 3 Veterinary Teaching Hospitals. The informed consent of the head of each clinic/hospital was obtained prior to the study.

Study Design

The study was a retrospective cross-sectional case analysis where clinical data were extracted from case records between January, 2010 and December, 2014. Cases inclusion criterion was dogs that were diagnosed with CPE based on either presumptive and/or laboratory diagnoses. Data obtained from individual case record files included patients' characteristics such as age, body weight, breed and sex. In addition, details of medications for each patient, including drugs administered, and diagnostic methods were extracted. Furthermore, the dosage regimen data such as dose/amount, frequency, duration and routes of administration of gentamicin for each patient per encounter was obtained from the clinical records.

Data were analyzed employing the method earlier described by Shea *et al*. (2011). The average number of drugs prescribed per encounter was computed to measure the degree of polypharmacy. This was done by dividing the total number of different drug products prescribed or administered by the total number of encounters. The prescription rate of drug by category and subsequent individual drugs in a category were obtained by dividing the number of patient encounters in which the class of drug was prescribed or administered by the total number of encounters surveyed. Also, the number of encounters in which the correct dose of injectable gentamicin was administered was obtained in order to measure the correctness of gentamicin medication.

RESULTS

Extraction of the reported cases of CPE between January, 2010 and December, 2014 from 20 small animal clinics in some parts of Nigeria yielded 704 cases. Of these, only

35 (5%) were diagnosed with CPE using canine parvovirus antigen test kit (rapid Enzyme chromatographic immunosorbent assay), whereas 609 (95%) were diagnosed presumptively based on circumstantial evidence such as age, vaccination history, exposure, vomiting, diarrhea and dehydration. Figure 1 illustrates extent of polypharmacy in the management of CPE in dogs during the period under review in some veterinary clinics/hospitals in the studied locations. Of the 687 cases reviewed, 133 (19.4%) were treated with less than 4 different drugs per encounter, whereas 461(67.1%) were at a single encounter, treated with 4-6 different drugs. On a single encounter, 90 (13.1%) and 3 (0.4%) of the patients were given 7-10 and more than 10 different drugs, respectively.

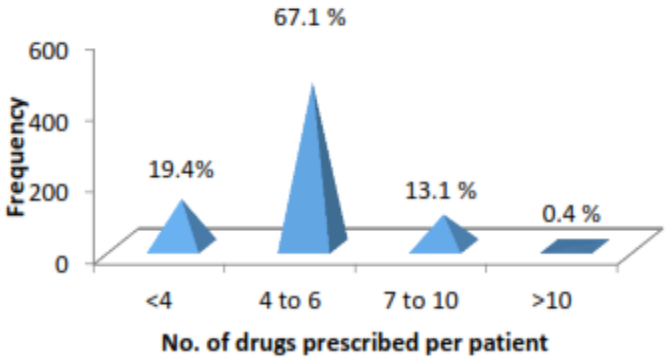

Figure 1: Polypharmacy practice in dogs on parvovirus enteritis management in some veterinary clinics in Nigeria from January, 2010 to December, 2014

Figure 2 shows that of the 2,482 drugs prescribed during the period, antimicrobial agents (AMC) were the most frequently prescribed, accounting for the prescription rate of 42.3% (1,050) followed by vitamins and minerals (VMS) which accounted for 25.3% (628) of the total prescriptions. The result also shows that anthelmintic (AHE), antiemetics (AEM), and gastrointestinal modulating drugs (GIM) accounted for 16.0% (398),

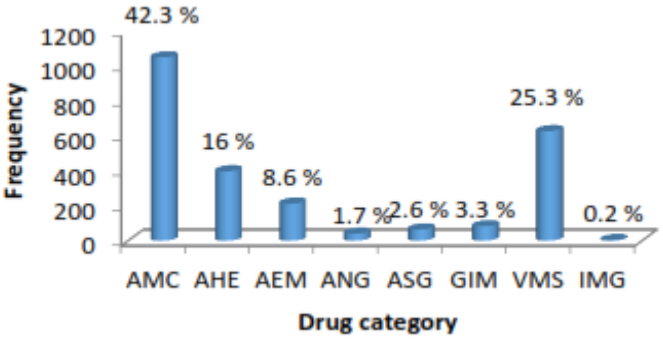

Figure 2: **C**ategory-wise drug prescription rates in dogs on parvovirus enteritis management in some small animal clinics in Nigeria from January, 2010 to December, 2014

Index: AMC (antimicrobial), AHE (anthelmintics), AEM (antiemetics), ANG (analgesics), ASG (anti-sialogogues), GIM (gastrointestinal modulators), VMS (vitamins and minerals), IMG (immunomodulators)

8.6% (216) and 3.3% (83) of the prescribed drugs, respectively. Furthermore, 2.6% (65), 1.7% (41) and 0.2% (4) of the total prescriptions were anti-sialogogues (ASG), analgesics (ANG) and immunoglobulin (IMG), respectively. Individual antimicrobial agents prescribed for dogs with CPE within the study period are shown in Figure 3. This result shows that of the 1050 antimicrobial agents prescribed to the study population, gentamicin (GEN) was the most frequently prescribed with a prescription rate of 23.8% (250), closely followed by metronidazole (MET) and oxytetracycline (OTC) which accounted for 20.0% (210) and 17.6% (186) prescription rates, respectively. Amoxicillin (AMX), sulphadimidine (SUP) and trimethoprim (TMP) accounted for 12.6% (132), 6.5% (68) and 4.7% (39), respectively. The 7 least prescribed antimicrobial agents in this population were penicillin (PEN) alone or with streptomycin (PES), enrofloxacin (ENR), amikacin (AMK), ceftriaxone (CET), chloramphenicol (CAM) and cefuroxime (CEF), each with a prescription rate less than 2.0%.

Result in Figure 4 shows that the most

commonly used gastrointestinal modulator was mist kaolin (MK) with a prescription rate of 58.0% (48). Prescription rates for ranitidine (RANITID: diphenoxylate), Lomotil® (LOM: diphenoxylate and atropine suphate), and Imodium® (loperamide), were 28.0% (23), 9.0% (8) and 5.0% (4), respectively.

Of the 41 prescriptions of analgesics for puppies with CPE, 68.0% (28) were piroxicam (PRX) injectable, 29.0% (12) diclofenac (DCF) injectable and 3.0% (1) was ibuprofen (IBF) tablet (Figure 5).

Result of gentamicin dose per body weight (mg/kg) in dogs on CPE management within the period under review is presented in Figure 6. Of the 250 gentamicin prescriptions, 57.0% (143) and 30.0% (74) accounted for doses less than 6mg/kg and 6-9 mg/kg, respectively. In addition, 6.0% (14) and 7.0% (19) of the prescriptions were administered at dose levels of 10-12mg/kg and above 12mg/kg, respectively. The average dose was 11.65mg/kg (0.1-26.7mg/kg).

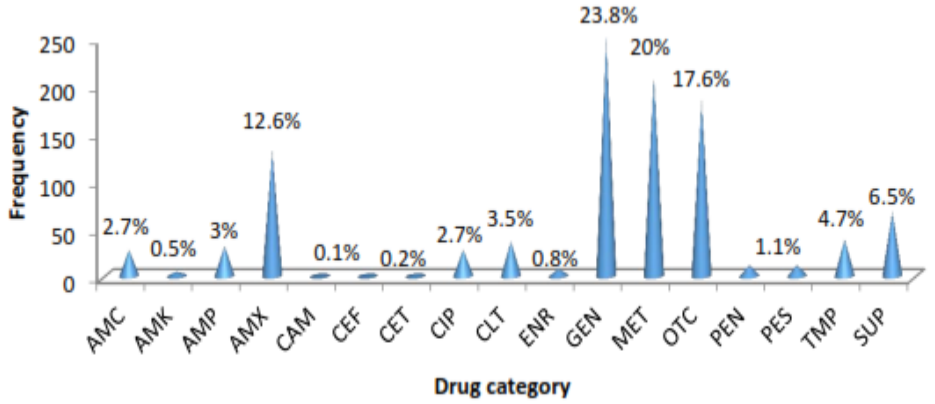

Figure 3: Prescription frequencies of antibiotics in dogs on parvovirus enteritis management in some small animal clinics in Nigeria from January, 2010 to December, 2014 (n=1050)

Index: AMC (amoxicillin/clavulanate), AMK (amikacin), AMP (ampicillin), AMX (amoxicillin), CAM (chloramphenicol), CEF (cefuroxime), CET (ceftriaxone), CIP (ciprofloxacin), CLT (chlortetracycline), ENR (enrofloxacin), GEN (gentamicin), MET (metronidazole), OTC (oxytetracycline), PEN (penicillin), PES (penicillin/strepomycin), TMP (trimethoprim), SUP (Sulphadimidine)

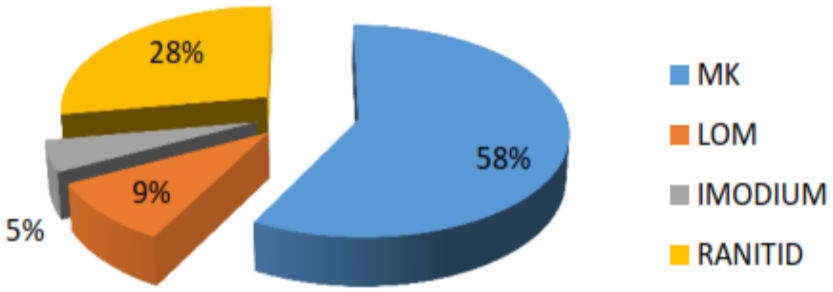

Figure 4: Prescription rate of gastrointestinal modulators for dogs with parvovirus enteritis in some veterinary clinics in Nigeria from January, 2010 to December, 2014

Index: MK (mist kaolin), LOM (lomotil), RANITID (ranitidine)

DISCUSSION

Multiple drug prescription (polypharmacy) has been reported to increase the risk of adverse drug-drug interactions, therapeutic failure and increase in the cost of treatment (Zuckermann, 2007; Bjerrum and Gonzalez, 2008; Kirsten *et al*., 2010). This study revealed that 67.1% of the patients were administered 4-6 different drugs per encounter which is above the recommended limit of 2 at a time for human (Isah *et al*., 2004). No such limit has been set for animals; however, the objective of this limit in human is simply to reduce drug-drug interactions and the effects on safety and

therapeutic outcome which applies to animals as well. In human patients with unspecified clinical conditions in Nigeria, 3.0-3.8 drugs per prescription have been reported (Tamuno and Fadare, 2012) which is comparable to our finding in dogs diagnosed with CPE. Consequently, polypharmacy, as demonstrated in this study could increase the risk of drug interactions and treatment cost. This may perhaps result in medication cascade effect as well as therapeutic duplication errors. This could have contributed to the poor therapeutic outcomes common in CPE management. However, polypharmacy is often associated with the management of critically ill patients where several drugs are used concomitantly to alleviate associated symptoms (Veehof *et al*., 2000). This is applicable to CPE patients where the aim is usually to manage a range of clinical symptoms associated with the illness, such as diarrhea, vomiting, secondary bacterial infections and pains. Consequently, fluids and electrolytes, anti-diarhoeics, antiemetics, antibiotics and analgesics are frequently and concurrently required for effective management of this condition (Appel *et al*., 1979). It is evident that polypharmacy is inevitable in CPE patients; nevertheless, considering the associated increased risk of adverse drug reactions that rises exponentially with the number of concomitant drugs used and interactions that may blur the intended effects of the drugs on the disease, the choice of drugs and dosage regimens must be appropriate and prudent.

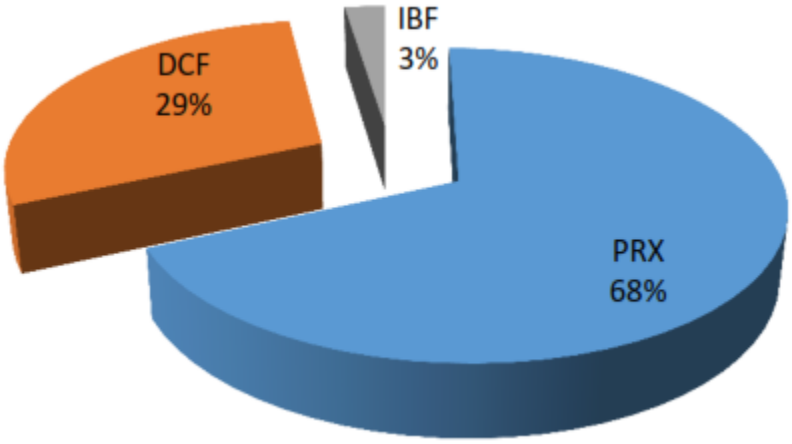

Figure 5: Prescription rates of analgesics in dogs with parvovirus enteritis in some veterinary clinics in Nigeria
Index: DCF (diclofenac), IBF (ibuprofen), PRX (piroxicam)

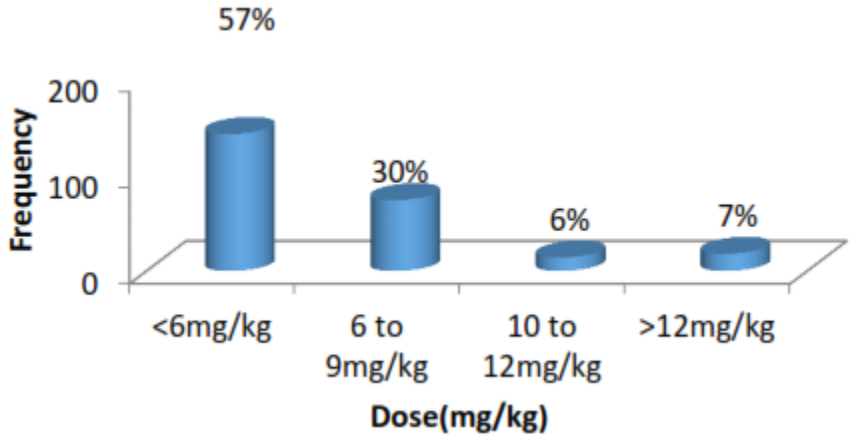

Figure 6: Gentamicin dosages in dogs on parvovirus enteritis management in some small animal clinics in Nigeria from January, 2010 to December, 2014

There is currently no specific treatment against CPE, nonetheless, good survival rates could be achieved with appropriate supportive treatment protocols involving different categories of drugs. This study shows that prescription rate of antimicrobials in dogs diagnosed with parvovirus enteritis ranked highest amongst other drug categories within the period under review (January, 2010 - December, 2014). This gives credence to an earlier

report that antimicrobial agents remain one of the most frequently prescribed drugs in human and veterinary medicine worldwide, and that they are empirically frequently considered for patients with acute hemorrhagic diarrhea (WHO, 1993). All the patients were administered at least one antimicrobial agent; however, there was no documented evidence (bacteriology result) to show that any of them had bacterial infection. Again, this study shows that of the 1050 antibiotics prescriptions, gentamicin ranked highest, accounting for 23.4% (250). This observation, to some extent is at variance with Shea *et al*. (2011) who reported that amoxicillin-clavulanate (18.3%); cefazolin/cephalexin (18.3%), enrofloxacin (16.7%), ampicillin/amoxicillin (14.9%) and doxycycline (11.2%) were the most frequently prescribed antibiotics in an undisclosed small animal clinic in the United States of America. However, the study was not specific to a disease condition as it applies to this study.

The disrupted intestinal mucosa barrier common in dogs with parvovirus enteritis predisposes them to a significant risk of developing sepsis due to the translocation of enteric bacterial organisms and/or toxins into the systemic circulation (Kahn, 2010). Furthermore, empirical antibiotic therapy before culture and sensitivity results is frequently considered for patients with acute hemorrhagic diarrhea to prevent deterioration of symptoms. These to a larger extent explain the observation in the present study that antibiotics medications were not guided by culture and sensitivity. In addition, the non-availability of functional diagnostic laboratories in majority of these veterinary centers, including the Veterinary Teaching Hospitals, and/or the associated cost when most clients may not be willing or unable to incur the financial cost, could have been additional contributing factors.

The choice of antibiotics may perhaps be informed by clinical presentation, culture and sensitivity result, spectrum of activity, safety, availability and cost. The high cost and scarcity of amikacin, cefazolin and ceftriaxone might have contributed to their low prescription rates observed even though they are as well effective as gentamicin and amoxicillin which are readily available and comparatively cheaper. Enrofloxacin, a fluoroquinolone for animals exclusively, is well known to cause damage to growing cartilage (erosive arthropathies), thus contraindicated in growing animals (Brown, 1980). This study has demonstrated that the average age of dogs managed for CPE was 5.9 months indicating that most of them were growing puppies. This perhaps could reasonably explain its very low prescription rate as observed, even though it is known to be an effective wide-spectrum bactericidal antibiotic for treating mixed infections (Vancutsem *et al*., 1990). One of the protozoan infections commonly associated with CPE is *Giardia spp* which metronidazole remains a mainstay drug for treatment (Vesy and Peterson, 1999; Kahn, 2010). This again explains the observed high prescription frequency of this agent for this population. Again, metronidazole is an antimicrobial agent used in the treatment of anerobic infections, including *Clostridia spp* which is associated with CPE (Lamp, 1999). Amoxicillin is one of the antibiotics of choice for an "unknown target infection" because it is relatively safe, inexpensive with a relatively broad spectrum of activity. Thus, these make it an antibiotic of choice for empirical use (Black *et al*., 2009; Shea *et al*., 2011). This possibly explains why it was among the five most prescribed antibiotics for dogs with CPE.

Concurrent intestinal parasite burden such as helminths, *Giardia spp* or *Eimeria spp* act as additional stress factors and can potentially worsen the severity of CPE (Prittie, 2004). These intestinal parasites have also been reported to enhance intestinal cell turnover, thereby increasing the rate of parvovirus infection with consequent intestinal epithelial cells destruction (Humm and

Hughes, 2009). It is therefore imperative to identify and eliminate these parasites. However, this study revealed that only 16.0% of the cases were prescribed anthelmintics, thus implying inadequate or under prescription.

Hydrated aluminum silicate (kaolin) has been traditionally used internally to control diarrhea. When administered orally, it adsorbs substances from the gastrointestinal tract and increases the bulk of feces (Bowman, 2012). Anti-diarrheal preparations containing kaolin have been used in the treatment of enteritis, cholera, and dysentery but not recommended as a sole agent in treating infectious diarrhea since it has no intrinsic antibacterial activity (Kahn, 2010). Nevertheless, enteral administrations have been reported to be effective in the treatment of systemic endotoxemia in an animal model (Gardiner *et al*., 1993). This study revealed that kaolin was never prescribed without antibiotics in any of the cases. The highest prescription rate of kaolin when compared with other gastrointestinal modulating drugs observed in this study could be to prevent the apparent endotoxemia by adsorbing endotoxins produced by enteric bacteria organisms, and dehydration due to diarrhea common in dogs with CPE. Although there is no clinical report establishing the clinical benefit for their use in the management of diarrhea in animals, it is often given to small animals, such as foals, calves, lambs as well as kids at a recommended dose of 1-2mL/kg *per os* 4 times daily (Kahn, 2010). Kaolin is highly insoluble and is not absorbed systemically, for this reason it is not usually associated with severe toxicity. Consequently, the administration of mist kaolin orally for controlling diarrhea and possible reduction of endotoxemia in dogs with CPE as observed is appropriate.

Ranitidine is a substituted aminoalkylfuran compound that is a selective and competitive antagonist of histamine-2 (H_2) receptors in the gastric parietal cells resulting in decreased gastric acid secretion triggered by histamine (Brittain and Daly, 1981; Broqden *et al*., 1982; Hoogerwerf and Pasricha, 2001). It is therefore used as an anti-ulcer drug in human and animals. At present, H_2-receptors are known to be significantly distributed only on the parietal cells of the gastric mucosa, mast cells, cardiac muscles and the lungs (Parsons and Ganellin, 2006; Naoyuki *et al*., 2014). Also, there is no empirical report describing direct or indirect involvement of H_2-receptor in the pathogenesis of parvovirus enteritis and involvement of the gastric mucosae other than its effect on small intestines. Consequently, prescription of ranitidine for parvovirus enteritis as observed in this study is irrational. This is because gastrointestinal tract pathologic lesion in CPE is mainly restricted to the small intestine characterized by erosion of the intestinal epithelial cells (Black *et al*., 1979; Otto Drobatz, 1997). In addition, considering the pharmacoeconomic aspect, its prescription in this population will be an unnecessary additional cost to the client.

Persistent vomiting common in parvovirus-infected dogs leads to fluid and electrolyte loss, interferes with nutritional support, precludes oral administration of medications, and puts the patient at risk of pneumonia and esophagitis (Kahn, 2010). Anti-emetic medications, including metoclopramide are therefore essential to avert the associated severe emesis in addition to limiting the preceding nausea, consequently, the patient is able to resume eating at an earlier stage of the disease. However, this study shows that antiemetics accounted for only 8.5% of the total drug categories commonly administered to dogs with CPE. Since majority of the cases were presented with vomiting, antiemetics were generally under-prescribed in this population. Dogs with CPE often exhibit significant visceral pains, with ileus being a common differential diagnosis. This requires the use of analgesics to control the

abdominal pain. However, non-steroidal anti-inflammatory drugs (NSAIDs) are contraindicated for pain management in dogs with parvovirus enteritis because of their ulcerogenic potential and the fact that they increase the risk of acute renal injury in dehydrated patient (Tripathi, 2008), which is consistent in dogs with parvovirus enteritis. Result from this study demonstrated that all the analgesics used were NSAIDs, mostly piroxicam, diclofenac and ibuprofen. This demonstrates irrational drug use in this clinical condition. Opioids, such as fentanyl are the preferred analgesics, however higher doses could worsen ileus and cause sedation. Effective therapeutic dose regimen of gentamicin for dogs is 6-12mg/kg to be administered once daily, by intramuscular or intravenous route (Kahn, 2010). In order to minimize adverse effects and optimize efficacy, treatment duration not exceeding 5 days had been recommended (Gberindyer *et al*., 2015). However, the present study revealed that of the 250 gentamicin prescriptions for dogs with CPE, 57.0% were below 6mg/kg body weight, indicative of under-dosing. Nevertheless, 30.0% of the administered doses were within the recommendation. This in addition has demonstrated the irrational practice in respect to dose regimen. This could be due to the fear of adverse effects (nephrotoxicity and ototoxicity) commonly associated with gentamicin. Under-dosing of antibiotic, which constitute irrational antibiotic use could result in therapeutic failure and emergence of drug resistant bacterial strains due to under-exposure. Thus, the study has sufficiently demonstrated that there is generally poor prescription attitude in the management of CPE in the study locations. This mostly involved management of the associated secondary bacterial infections, diarrhea, vomiting and pain.

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