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Phase I Dose Escalation of Single-Agent Vinblastine in Dogs

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Background: Vinblastine (VBL) is commonly used in dogs at a dosage of 2.0 mg/m^2. The minimal toxicity observed at this dosage indicates that higher dosages might be well tolerated.

Hypothesis: The maximum tolerated dosage (MTD) for a single VBL treatment is higher than the previously published dosage of 2.0 mg/m^2.

Animals: Twenty-three dogs with lymphoma or cutaneous mast cell tumors.

Methods: Dogs received 1 single-agent VBL treatment IV. The starting dosage was 3.0 mg/m^2, and dosages were increased in increments of 0.5 mg/m^2 in cohorts of 3 dogs. Hematologic toxicity was assessed with weekly CBCs. Gastrointestinal toxicity was assessed from medical histories from owners. Once the MTD was determined, additional dogs were treated with VBL at that dosage. Dogs whose cancers responded to VBL continued to receive treatments q2–3 weeks.

Results: VBL dosages ranged from 3.0 to 4.0 mg/m^2. Neutropenia was the dose-limiting toxicity, with the nadir identified 7 days after treatment and resolving by 14 days after treatment. The MTD was 3.5 mg/m^2. Sixteen dogs were treated at this dosage, and 3 experienced severe toxicity characterized by asymptomatic grade 4 neutropenia, febrile grade 4 neutropenia, and death. Gastrointestinal toxicity was mild and self-limiting. Preliminary evidence of antitumor activity was identified in 2 of 12 dogs with lymphoma treated at the MTD.

Conclusions and Clinical Importance: In dogs, single-agent VBL is well tolerated at a dosage of 3.5 mg/m^2 IV. At this dosage, the minimum safe treatment interval is q2 weeks, and adjunct treatment with prophylactic antibiotics should be considered.

Key words: Canine; Chemotherapy; Oncology; Oncology treatment.

Vinblastine (VBL) is an antimicrotubule chemotherapeutic. Like all vinca alkaloids, its principal mechanism of cytotoxicity is mediated by binding to tubulin and disrupting microtubule formation, particularly the microtubules comprising the mitotic spindle apparatus.[1–3] In veterinary oncology, VBL is used most commonly to treat dogs with advanced-stage or high-risk mast cell tumors.[4–9] Early reports speculated about its usefulness for treating canine lymphoma,[1,2] but to date there are no published studies to support these statements.

The dose-limiting toxicity of VBL in dogs is neutropenia.[1,2,4–8,10,11] Adverse gastrointestinal effects are seen less commonly when conventional dosages are given,[4–8] but they can be severe in dogs with concurrent underlying gastrointestinal disease[6,8] or when higher doses are administered.[10] In a preclinical study, 47 healthy dogs received single VBL treatments at dosages ranging from 0.2 to 0.5 mg/kg.[10] From the range of body weights provided, the range of potential dosages based on body surface area was 4.1–15.4 mg/m^2. The mean neutrophil nadir was 1,200 cells/μL for dogs treated at 0.20 mg/kg and 600 cells/μL for dogs treated at 0.25 mg/kg. Mortality rates for these groups were 27% (9 of 34 dogs) and 43% (3 of 7 dogs), respectively. All 6 dogs treated at dosages $\geq$0.3 mg/kg died. At all dosages, deaths were attributed to a combination of severe neutropenia and fulminant diarrhea.

Most clinical studies using single-agent VBL (with or without prednisone) have used a dosage of 2.0 mg/m^2 every 1–2 weeks.[4–8] The neutrophil count reaches its nadir approximately 1 week after VBL administration.[1] Therefore, with weekly administration dogs might be receiving treatments around the time when the neutrophil count has reached its nadir from the previous dose. Despite this, fewer than 7% of dogs treated at this dosage experienced severe neutropenia, characterized by a neutrophil nadir $<$500 cells/μL, or febrile neutropenia.[4–8] Additionally, the only dogs that experienced unacceptable gastrointestinal effects had pre-existing underlying gastrointestinal disease.[6,8]

The commonly used VBL dosage of 2.0 mg/m^2 was derived empirically.[12,13] A phase I dosage escalation study to identify the maximum-tolerated dose (MTD) has not been performed. Moreover, given the low incidence of dose-limiting toxicity when dogs receive 2.0 mg/m^2 VBL, the MTD likely is higher. Dose-response curves for antitumor benefit usually are steep; increasing the VBL dosage might improve clinical response rates and response durations.[14]

The primary goal of this study was to complete a dose escalation trial and determine the MTD for a single VBL treatment in dogs. Once the MTD was established, additional dogs were treated with VBL at that dosage to further characterize the associated toxicity and determine its potential usefulness for treating canine lymphoma.

Materials and Methods

Study Subjects

Client-owned dogs that presented to the Cornell University Hospital for Animals, Animal Cancer Specialists, or the Foster Hospital for Small Animals at Tufts Cummings School of Veterinary

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Medicine with histologically confirmed mast cell neoplasia or multicentric lymphoma were included in this study. To be eligible, dogs must not have received myelosuppressive chemotherapy or prednisone for at least 2 weeks before treatment with VBL, and their neutrophil count had to be above the lower limit of the normal reference range for that institution. Dogs could not have any gastrointestinal signs at the time of treatment. Concurrent diseases were allowed at the discretion of the attending clinician as long as it was thought that they would not increase the likelihood or severity of VBL-associated toxicity. Client consent was obtained before enrollment in the study.

Treatment and Assessment of Toxicity

On the day of treatment, each dog had a baseline physical examination and CBC performed. Additional diagnostic tests were performed only if requested by the attending clinician. Each dog then received a dose of VBL[a] as a rapid IV bolus. VBL dosage was determined using the dose escalation scheme detailed below. Trimethoprim-sulfadiazine[b] (15 mg/kg PO q12h) was administered prophylactically for 14 days starting the day after VBL treatment. Dogs returned weekly for physical examination and CBC for 2 weeks or until the neutrophil count returned to within normal limits, whichever was longer. At each visit, owners were asked to provide information regarding any gastrointestinal or other adverse effects observed at home. Toxicities were graded using the Veterinary Cooperative Oncology Group Common Terminology Criteria for Adverse Events v1.0 (VCOG-CTCAE, see Appendix 1).[15] Severe toxicity was defined as asymptomatic grade 4 neutropenia; febrile neutropenia; ≥grade 3 anorexia, vomiting, or diarrhea; or death.

The initial VBL dosage was set at 3.0 mg/m^2, and it was then escalated in cohorts of 3 dogs. If none of the 3 dogs treated in a given cohort experienced severe toxicity, the dosage for the next cohort was escalated by 0.5 mg/m^2. If one of the dogs experienced severe toxicity, an additional 3 dogs were treated at that dosage. If no additional dogs experienced severe toxicity at that dosage, then the escalation was resumed. If ≥2 dogs in a cohort experienced severe toxicity, additional enrollment in that cohort was stopped. The MTD was defined as the highest dosage that resulted in ≤1 of 6 dogs experiencing severe toxicity.

Response to therapy was not a primary end-point for this study. However, if a dog achieved a complete remission, characterized by complete disappearance of all measurable disease, or a partial remission, characterized by >50% but <100% reduction in all measurable disease, then VBL treatments were continued at an every 2- or 3-week interval for as long as the response was maintained. Intrapatient dosage escalations were not permitted. However, if a patient experienced severe toxicity, any subsequent VBL doses for that patient were decreased by 25%. A CBC was performed before each subsequent treatment, but weekly CBCs were not performed between subsequent treatments unless there was previous documentation of severe neutropenia necessitating dosage reduction.

Results

Twenty-three dogs were enrolled in this trial. Seventeen dogs were presented to Cornell University, 5 to Tufts University, and 1 to Animal Cancer Specialists. Breeds included were mixed (n = 8), Golden Retriever (5), Rottweiler (3), Boxer (2), Labrador Retriever (1), Mastiff (1), Boston Terrier (1), Cocker Spaniel (1), and Airedale (1). Twelve dogs were male (8 castrated) and 11 were female (9 spayed). Median age at the time of VBL treatment was 9 years (range, 4–14 years), and median weight was 35.5 kg (range, 11.6–54.8 kg). Eight dogs were diagnosed with mast cell tumors. Of these, 3 did not receive any chemotherapy before VBL, 3 received single-agent CCNU (lomustine), and 2 received CCNU plus prednisone. Fifteen dogs were diagnosed with lymphoma. Of these, 12 initially were treated with L-CHOP (L-asparaginase, cyclophosphamide, doxorubicin, vincristine, and prednisone), 2 were treated with COP (cyclophosphamide, vincristine, and prednisone), and 1 was treated with a combination of L-asparaginase, doxorubicin, and MOPP (mustargen, vincristine, procarbazine, and prednisone). Dogs that completed their L-CHOP or doxorubicin-based protocol before relapse resumed L-CHOP, and dogs that failed COP were rescued with doxorubicin-based protocols. Therefore, all dogs were confirmed to be resistant to CHOP drugs before starting rescue therapy. Upon failing CHOP drugs, 3 received VBL next. The remaining dogs received a variety of other rescue drugs before receiving VBL: L-asparaginase (n = 11), CCNU plus cyclophosphamide (9), MOPP (5), CCNU (3), mitoxantrone (1), and prednisone (1).

Table 1. Severity of adverse hematologic events following administration of a single dose of vinblastine to dogs.

VBL Dose (mg/m^2)	# of Dogs	Grade of Neutropenia[a]					Grade of Thrombocytopenia[a]				
		0	1	2	3	4	0	1	2	3	4
3.0	3	1	1	1	0	0	2	1	0	0	0
3.5	16[b]	4	3	4	2	2	10	2	1	0	0
4.0	4	1	1	0	1	1	4	0	0	0	0

[a]See Appendix 1 for grading criteria.

[b]One dog died before a post-vinblastine CBC was obtained. Accurate platelet counts were not available for an additional 2 dogs in this cohort.

VBL, vinblastine.

Three dogs received VBL at a dosage of 3.0 mg/m^2. This dosage was well tolerated, with minimal hematologic or gastrointestinal toxicity (Tables 1 and 2). Six dogs received VBL at a dosage of 3.5 mg/m^2, and 1 experienced severe toxicity characterized by asymptomatic grade 4 neutropenia. Four dogs received VBL at a dosage of 4.0 mg/m^2, and 2 experienced severe toxicity. One dog developed asymptomatic grade 4 neutropenia, and another experienced febrile grade 3 neutropenia that resolved quickly with hospitalization and supportive care. From these results, the MTD of VBL was determined to be 3.5 mg/m^2.

An additional 10 dogs were subsequently treated with VBL at a dosage of 3.5 mg/m^2. One dog died 4 days after treatment. This dog was diagnosed with lymphoma, and at the time of VBL treatment had a large tumor burden including pulmonary infiltration and already had failed 2 rescue protocols. The owner reported that energy level and respiratory effort improved slightly before death. Adverse gastrointestinal signs were not observed.

Table 2. Severity of adverse gastrointestinal events following administration of a single dose of vinblastine to dogs.

VBL Dose (mg/m^2)	# of Dogs	Grade of Anorexia[a]						Grade of Vomiting[a]						Grade of Diarrhea[a]					
		0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5
3.0	3	1	1	1	0	0	0	2	1	0	0	0	0	3	0	0	0	0	0
3.5	16	9	1	5	1	0	0	11	4	1	0	0	0	12	4	0	0	0	0
4.0	4	2	0	2	0	0	0	4	0	0	0	0	0	3	1	0	0	0	0

[a]See Appendix 1 for grading criteria.
VBL, vinblastine.

Adverse clinical signs commonly associated with sepsis, such as anorexia, lethargy, or pyrexia, were not observed either. A necropsy was not performed. Of the remaining 9 dogs, 1 experienced severe toxicity characterized by febrile grade 4 neutropenia, grade 3 anorexia, and grade 2 vomiting. This dog was hospitalized, and clinical signs resolved quickly with supportive care including IV fluids, antibiotics, antiemetics, and gastroprotectants. Therefore, in total, 3 of the 16 dogs (19%) treated with VBL at a dosage of 3.5 mg/m^2 experienced severe toxicity. In one of these dogs, the toxicity was asymptomatic; 2 of 16 dogs (13%) experienced severe clinical signs in association with VBL treatment.

Neutropenia was identified as the dose-limiting toxic event. Neutropenia of some degree was recognized in 16 of 22 dogs tested (73%), and in all 16 dogs the neutrophil nadir was identified 1 week after treatment. Fifteen of these dogs had a CBC repeated 2 weeks after treatment, and in all dogs the neutrophil count had returned to within normal limits. A week 2 CBC was not available for the remaining dog, but it experienced asymptomatic grade 1 neutropenia 1 week after treatment and mild neutrophilia (14,000 neutrophils/μL) 3 weeks after treatment.

Gastrointestinal toxicity of some kind was identified in 13 of the 23 dogs (57%). Some dogs experienced multiple concurrent adverse effects, but anorexia was the most common toxic event, occurring in 11 dogs (48%). Vomiting was observed in 6 dogs (23%), and diarrhea in 5 dogs (22%). Over the range of VBL dosages evaluated, there was no obvious dose dependency on the frequency or severity of adverse gastrointestinal effects. Only 1 dog experienced severe gastrointestinal toxicity (grade 3 anorexia and grade 2 vomiting), but as previously discussed this dog likely was septic with febrile grade 4 neutropenia, and all clinical signs quickly resolved with supportive care.

Fifteen dogs received only 1 dose of VBL, 3 dogs received 2 doses, 4 dogs received 3 doses, and 1 dog received 8 doses. Of the 8 dogs that received multiple doses, 1 was in the 3.0 mg/m^2 cohort, 6 were in the 3.5 mg/m^2 cohort, and 1 was in the 4.0 mg/m^2 cohort. VBL dosage was kept constant for 6 dogs. Two dogs in the 3.5 mg/m^2 cohort had 25% dosage reductions (2.62 mg/m^2) due to asymptomatic grade 3 and 4 neutropenia after their 1st treatment. At this new dosage, these dogs experienced asymptomatic grade 2 and 1 neutropenia, respectively. Overall, none of the dogs receiving multiple treatments experienced severe toxicity from any of their subsequent treatments, although CBCs were not performed consistently 1 week after all additional treatments.

Although there were no body weight restrictions for enrollment, by chance no dogs weighed <10 kg. Four dogs weighed between 10 and 20 kg. One of these dogs was enrolled in the 3.0 mg/m^2 cohort. It did not experience any neutropenia, but it did experience grade 2 anorexia and grade 1 vomiting. The remaining 3 dogs were enrolled in the 3.5 mg/m^2 cohort. One did not experience any neutropenia or adverse gastrointestinal effects; 1 experienced grade 1 neutropenia and grade 2 anorexia; 1 experienced grade 4 neutropenia, grade 2 anorexia, grade 1 vomiting, and grade 1 diarrhea. There were too few small dogs to perform statistical analyses, but there was no obvious relationship between body size and adverse effects. Additionally, the dogs in the 3.5 mg/m^2 cohort that experienced severe toxicity weighed 11.6, 33.5, and 54.8 kg.

Of the 15 dogs with CHOP-resistant lymphoma enrolled in this study, remissions were attained using single-agent VBL in 3 (20%). One dog in the 3.0 mg/m^2 cohort achieved a complete remission lasting for 48 days. Two dogs in the 3.5 mg/m^2 cohort attained partial remissions lasting for 28 and 41 days. Considering specifically the 12 dogs with CHOP-resistant lymphoma treated with VBL at the MTD, remissions were achieved in 2 (17%). Not all of the dogs with mast cell tumors included in this study had measurable disease at the time of enrollment, and therefore response information is not presented.

Discussion

Results of this study confirm the dose-limiting toxicity associated with VBL in dogs to be neutropenia. Gastrointestinal toxicity, although common, usually was mild and did not warrant medical intervention. The maximum tolerated single dose of VBL was 3.5 mg/m^2. A total of 16 dogs received this dose, and severe adverse effects were observed in 3 dogs (19%). One of these dogs was asymptomatic for its neutropenia. Serious clinical consequences resulted in 2 dogs (13%)—1 dog required hospitalization for presumed sepsis and 1 dog died 4 days after treatment. The dog that died did not exhibit any adverse effects of treatment before death; in fact, its owners reported improvement in clinical signs after receiving VBL. However, a necropsy was not performed, and considering its large tumor burden acute tumor lysis syndrome cannot be ruled out.[16] Therefore, to be conservative, we have assumed that this was a treatment-related

death. Even so, the level of toxicity observed at the MTD is considered acceptable and in agreement with the standards of clinical veterinary oncology.[17,18]

The neutrophil nadir consistently was identified 1 week after VBL administration, and the neutrophil count recovered to within normal limits by week 2. Additionally, in the dogs that received multiple treatments, no evidence of cumulative toxicity was identified. Based on these results, the recommended dosing interval for single-agent VBL given at a dosage of 3.5 mg/m^2 is every 2 weeks.

In people, intensive pretreatment with myelosuppressive chemotherapy can exacerbate the severity of the myelosuppression observed in subsequent protocols.[19] Although 20 of the 23 dogs included in this study had been treated previously with 1 or more chemotherapy protocols, this pretreatment was not thought to substantially influence the MTD because 2 of the previously untreated dogs were in the 4.0 mg/m^2 cohort and both experienced severe toxicity. Moreover, the treatment histories of the dogs included in this study accurately reflect those of dogs likely to be treated with VBL.

Small dogs were not intentionally excluded from this study, but none of the dogs weighed <10 kg and only 4 dogs weighed between 10 and 20 kg. Smaller dogs have been shown to experience increased toxicity when certain chemotherapy drugs are dosed based on body surface area, including doxorubicin, cisplatin, carboplatin, and melphalan.[20–23] A similar relationship between body weight and toxicity has not been reported in any of the previously published studies in which VBL was administered at a dosage of 2.0 mg/m^2 q1–2 weeks,[4–8] nor has one been reported for dogs treated with vincristine or vinorelbine.[17,24] The authors do not feel a routine dosage reduction below 3.5 mg/m^2 is warranted when treating small dogs, but they acknowledge that careful monitoring is indicated until experience is gained treating smaller dogs.

Oral trimethoprim-sulfadiazine was administered prophylactically to all dogs in this study. Although controversial, the use of prophylactic antibiotics in human oncology is a cost-effective way to prevent febrile neutropenia in high-risk patients.[25,26] The role of prophylactic antibiotic use needs to be better defined in veterinary oncology. However, a recent study in dogs with osteosarcoma or lymphoma treated with doxorubicin or doxorubicin plus L-asparaginase, respectively, showed that prophylactic treatment with trimethoprim-sulfadiazine significantly reduced the occurrence of nonhematologic toxicity, hospitalization, and poor performance.[27] Additionally, prophylactic antibiotic therapy has been successfully used in phase I studies in which severe neutropenia was anticipated.[28] Given the severe myelosuppression observed in the preclinical studies evaluating VBL in dogs,[10,11] the authors felt use of prophylactic antibiotics was warranted. The impact of prophylactic antibiotic administration on the incidence of febrile neutropenia cannot be determined from this study. However, given that 25% of the dogs treated with VBL at a dosage of 3.5 mg/m^2 developed grade 3 or 4 neutropenia, continued use of adjunct trimethoprim-sulfadiazine is justified.

The currently recommended single dosage of 3.5 mg/m^2 represents a 75% increase compared with the historically used dosage of 2.0 mg/m^2. Most cytotoxic chemotherapy drugs have very steep dose-response curves, indicating that a small change in drug dose might have a substantial impact on ability to control the patient's cancer.[14,29,30] In preclinical models, altering drug dose by 20–25% can affect cure rate by as much as 50%.[29] Additionally, many chemotherapy drugs have threshold doses that need to be exceeded for treatment to be efficacious. For example, when dogs with lymphoma received single-agent doxorubicin at dosages of either 30 mg/m^2 q3 weeks or 10 mg/m^2 q1 week, overall remission rates were comparable but median remission durations were 147 and 14 days, respectively.[31,32] A threshold effect has also been identified when vincristine is used to treat women with breast cancer.[30] A similar threshold effect might exist when using VBL, another vinca alkaloid. Threshold effects likely depend both on the drug and the tumor type, but, regardless of the underlying factors, the observation of threshold effects emphasizes the importance of administering drugs such as VBL at their MTD.

Another important concept in cancer treatment efficacy is dose intensity—the amount of drug delivered per unit time, expressed as mg/m^2/wk regardless of schedule. Dose intensity is predictive of remission rate and survival in people with several different forms of cancer, including breast cancer, non-Hodgkin's lymphoma, and small cell lung cancer.[29,30] Using the current VBL dosage recommendation of 3.5 mg/m^2 q2 weeks, the resulting dose intensity is 1.75 mg/m^2/wk. In previous reports in which VBL was administered at a dosage of 2.0 mg/m^2, treatments typically were administered weekly for 4 treatments and then every other week for an additional 4 treatments for an overall dose intensity of only 1.33 mg/m^2/wk.[4–8] For the 1st month of that protocol, however, the dose intensity was higher—2.0 mg/m^2/wk. Front-end-loaded regimens might be advantageous because they decrease the time for tumor regrowth when overall tumor burden is at its highest and reduce the likelihood of drug-resistant mutant cells developing.[29] Additional studies therefore are needed to determine the optimal dosing schedule when using a single-agent VBL protocol.

Response to therapy was not a primary end-point of this study, but because there are no previously published reports confirming the usefulness of VBL for treating canine lymphoma, it is interesting to note that 3 of 15 dogs (20%) achieved a complete or partial remission. Additionally, all of these dogs had failed a vincristine-containing protocol before receiving VBL, indicating a lack of total cross-resistance between these vinca alkaloids. A similar lack of cross-resistance between VBL and vincristine has been demonstrated in people with non-Hodgkin's lymphoma.[33,34] The underlying mechanism for this lack of total cross-resistance is not completely understood, but likely includes different binding affinities for tubulin resulting from variations in tubulin isotype as well as the type and concentration of microtubule-associated proteins.[3] Differences in cellular pharmacology might also play an important role. In vitro, VBL is taken up and

released more quickly from cells.[35–37] Additionally, VBL might be more likely to accumulate at other intracellular sites in addition to tubulin, such as in the lipid phase of the plasma membrane.[35–37]

Sample size in the present study was not large enough to accurately determine the true efficacy of single-agent VBL for resistant lymphoma; however, the reported response rate of 20% is not high enough to assume that single-agent VBL might be an effective rescue protocol. Still, it might be possible to effectively incorporate VBL into multiagent rescue protocols for resistant canine lymphoma. Each drug included in a multiagent protocol should have an overall response rate of 20–30% and preferably should induce complete remission in some fraction of treated patients.[14,38,39] Moreover, the lack of cross resistance between VBL and vincristine for canine lymphoma supports the potential utility of substituting VBL for vincristine in rescue protocols such as MOPP, BOPP, or LOPP (mustargen, carmustine [BCNU], or lomustine [CCNU], respectively, with vincristine, procarbazine, and prednisone) that typically are used after patients have failed vincristine-containing protocols such as CHOP or COP.[40,41] Additional studies are needed to confirm this hypothesis and better define the role of VBL when treating canine lymphoma.

In summary, VBL can be administered safely to dogs at a dosage of 3.5 mg/m^2 IV q2 weeks. This new dosing regimen offers both theoretical advantages and disadvantages compared with the historically used regimen of 2.0 mg/m^2 IV q1–2 weeks. Additional studies are needed to determine whether one of these dosing regimens is clinically superior to the other.

Footnotes

[a] Vinblastine, Abraxis, Schaumburg, IL
[b] Tribrissen, Interfarm, Hauppauge, NY

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Appendix 1

Table A1. Grading criteria used to assess adverse hematologic and gastrointestinal events following administration of a single dose of vinblastine to dogs (veterinary co-operative oncology group—common terminology criteria for adverse events v 1.0 [VCOG-CTCAE][15]).

Adverse Event	Criteria
Neutropenia	
0	≥3,400 neutrophils/μL
1	1,500–3,399 neutrophils/μL
2	1,000–1,499 neutrophils/μL
3	500–999 neutrophils/μL
4	<500 neutrophils/μL
Thrombocytopenia	
0	≥179,000 platelets/μL
1	100,000–178,999 platelets/μL
2	50,000–99,999 platelets/μL
3	15,000–49,999 platelets/μL
4	<15,000 platelets/μL
Anorexia	
0	None
1	Coaxing or dietary change required to maintain appetite
2	<3 days (d) duration, no significant weight loss
3	3–5 days, weight loss, nutritional supplementation needed
4	>5 days, life-threatening consequences
5	Death
Vomiting	
0	None
1	<3 episodes in 24 hours
2	3–5 episodes in 24 hours, <3 episodes/d for 2–5 days, SC/IV fluids for <1 day
3	>5 episodes in 24 hours, vomiting >4 days, IV fluids for >24 hours
4	Life threatening (eg, hemodynamic collapse)
5	Death
Diarrhea	
0	None
1	Increase of <2 stools/d over baseline
2	2–6 stools/d over baseline, SC/IV fluids <24 hours
3	>6 stools/d over baseline, incontinence, IV fluids >24 hours
4	Life threatening (eg hemodynamic collapse)
5	Death