

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Uyeki TM, Mehta AK, Davey RT Jr, et al. Clinical management of Ebola virus disease in the United States and Europe. *N Engl J Med* 2016;374:636-46. DOI: 10.1056/NEJMoa1504874

Title: Clinical Management of Ebola Virus Disease in the United States and Europe

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Supplementary Methods - Laboratory Assays

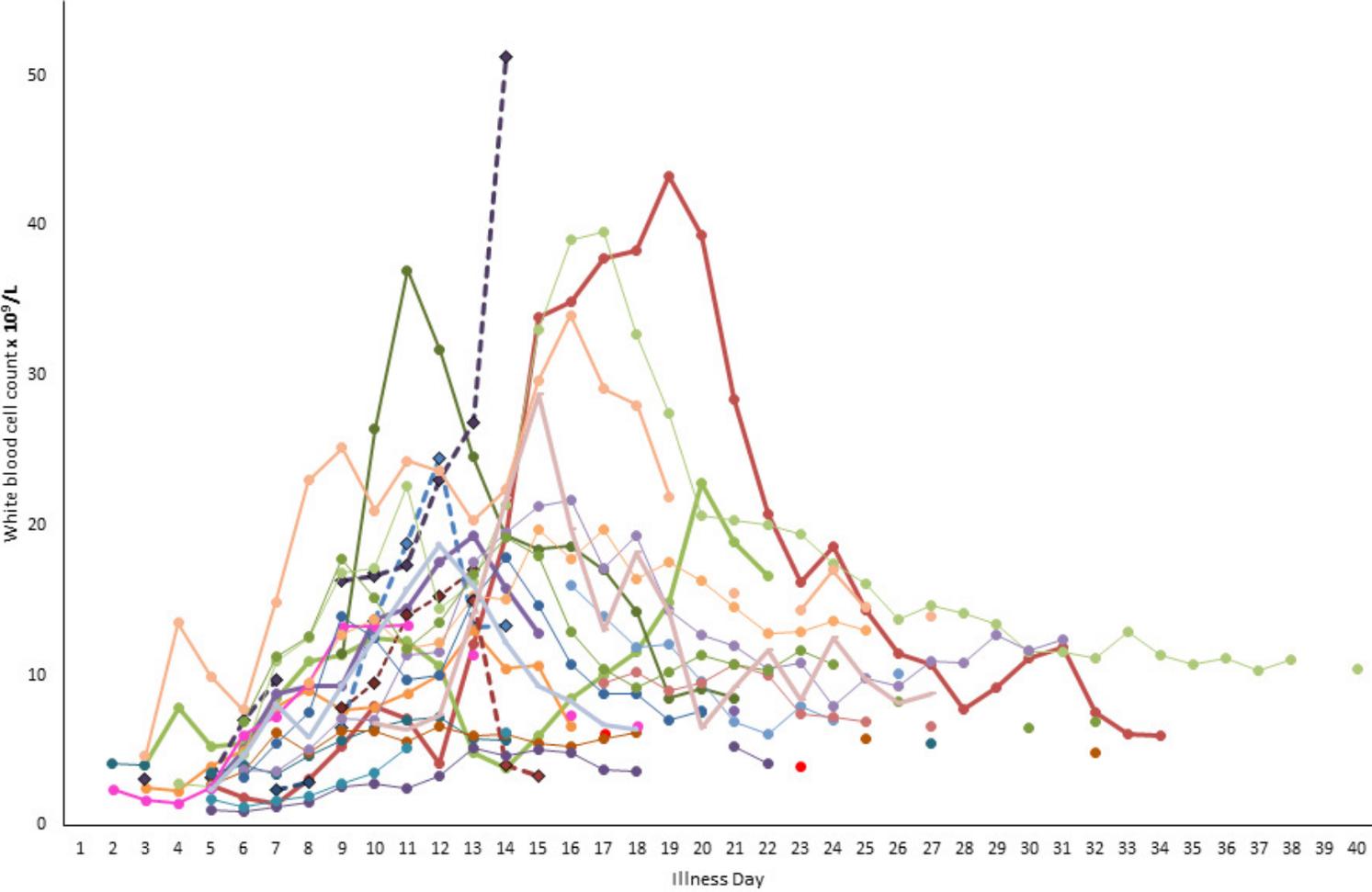
Point-of-care assays used at clinical sites included: for blood chemistry (Piccolo Xpress[®], Abaxis; iSTAT[®], Abbott Point of Care; SPOTCHEM-EZ[™], Arkray; Reflotron[®] Plus, Roche); for hematology (pocH-100i[™], Sysmex; KX21N[™], Sysmex; ABX Micros CRP 200, Horiba; epoc[®], Alere; ABX Micros ES 60, Horiba; COULTER Ac-T[™] diff, Beckman Coulter); for coagulation parameters (CoaguChek[®] XS system, Roche; iSTAT[®], Abbott Point of Care; CA-560, Sysmex; Simple Simon[®] PT-INR, Zafena; Cobas h 232, Roche CARDIAC; Hemochron[®] Signature Elite, Accriva; STA Compact[®], Diagnostica Stago; 4-channel Zeiss coagulometer, C. Zeiss); for blood gas analyses (ABL 800 Flex, Radiometer; ABL80 FLEX CO-OX, Radiometer; GEM[®] Premier[™] 4000, Instrumentation Laboratory; epoc[®], Alere; Gem[®] Premier[™] 3000, Instrumentation Laboratory; iSTAT[®], Abbott Point of Care); for urinalysis (CLINITEK Status[®], Siemens; Multistix[®] 10 SG Reagent Strips, Siemens); for respiratory pathogens (FilmArray[®] Respiratory Panel, BioFire Diagnostics); for gastrointestinal pathogens (FilmArray[®] Gastrointestinal Panel, BioFire Diagnostics); for blood culture (BD Bactec[™] FX40, Becton Dickinson); for malaria (BinaxNOW[®] Malaria, Alere; CareStart[™] Malaria Rapydtest[®], Apacor); and for HIV (OraQuick[®], OraSure Technologies; OraQuick ADVANCE[®] Rapid HIV-1/2 Antibody Test, OraSure Technologies).

RT-PCR assays for detection of Ebola viral RNA used to test clinical specimens from Ebola virus disease patients included: (RealStar[®] Filovirus RT-PCR Kit 1.0, Altona Diagnostics (with modifications to allow quantitative RT-PCR [1-3], Ebola Zaire (EZ1) rRT-PCR (Taq-Man[®]) Assay, U.S. Department of Defense [4]; CDC Ebola Virus NP Real-time RT-PCR Assay, U.S. Centers for Disease Control and Prevention [5] as previously described [6]; and an assay based upon previous reported methodology [7]).

EBOV load was quantitated in clinical specimens from Ebola virus disease patients using RealStar[®] Filovirus RT-PCR Kit 1.0, Altona Diagnostics [1-3,8] and in-house assays, including at national reference laboratories.

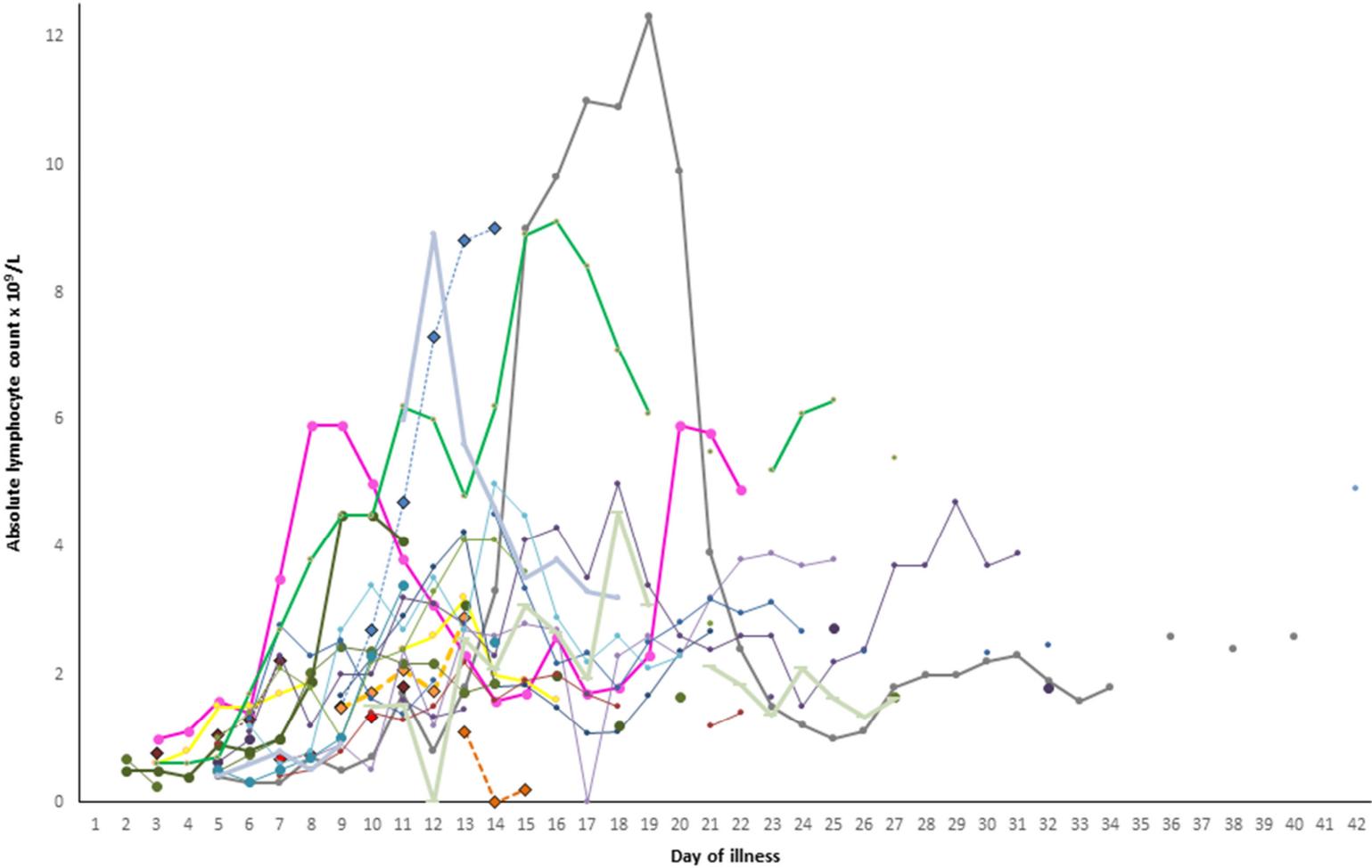
Serological assays for detection of Ebola virus antibodies (IgM, IgG) included the following: (enzyme-linked immunosorbent assays as previously described [5,9,10]; human anti-Zaire Ebola Virus Glycoprotein IgG/IgM ELISA kit (Alpha Diagnostic International [1,2]; and in-house immunofluorescence assays developed using Ebola virus Makona strain cultured in VERO E6 cells as antigen [2,3]).

Figure S1. Daily white blood cell counts for 27 Ebola Virus Disease patients hospitalized in Europe or the U.S.



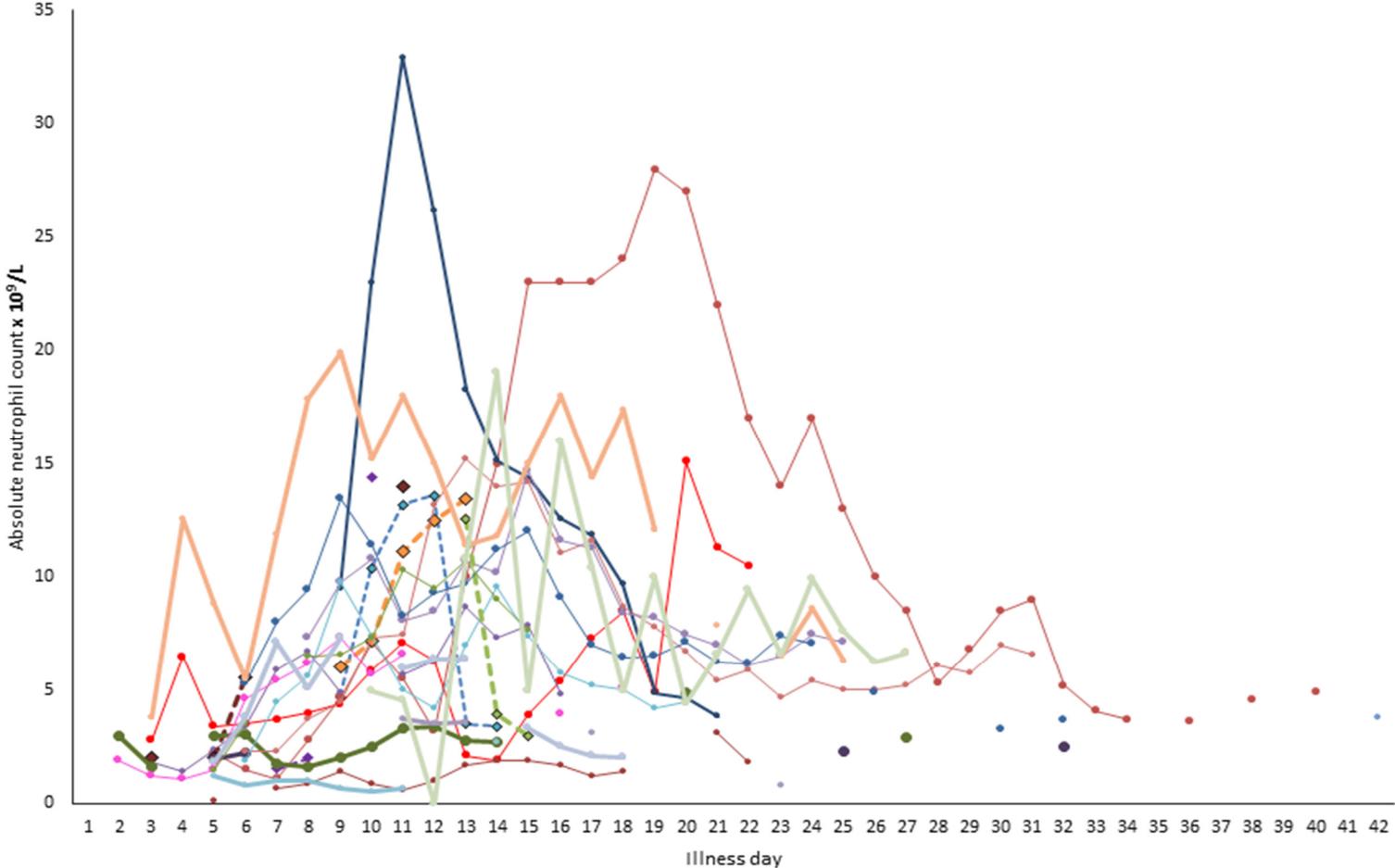
Fatal cases are denoted by diamond markers and dotted lines.

Figure S2. Daily absolute lymphocyte counts for 27 Ebola Virus Disease patients hospitalized in Europe or the U.S.



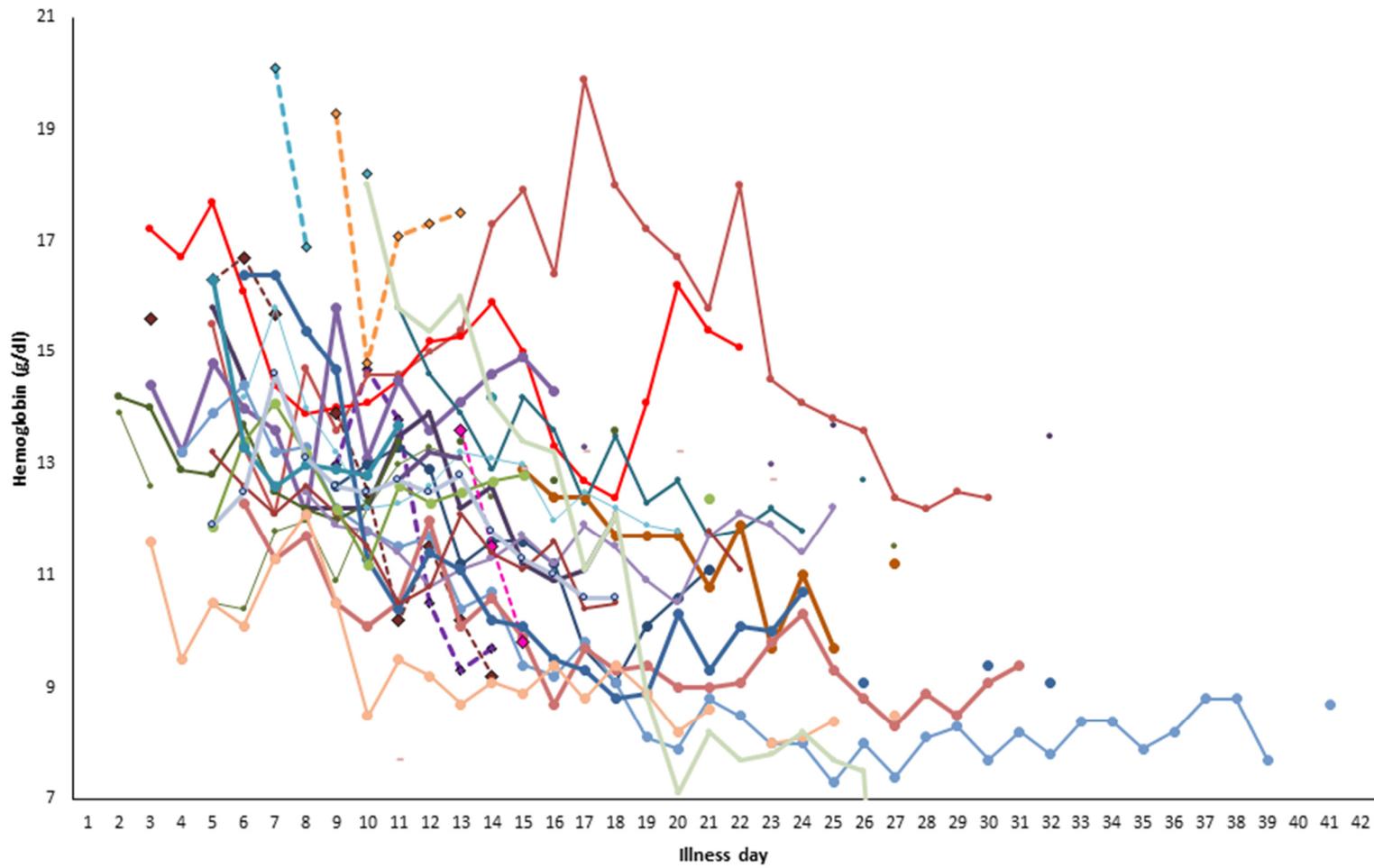
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Figure S3. Daily absolute neutrophil counts for 27 Ebola Virus Disease patients hospitalized in Europe or the U.S.



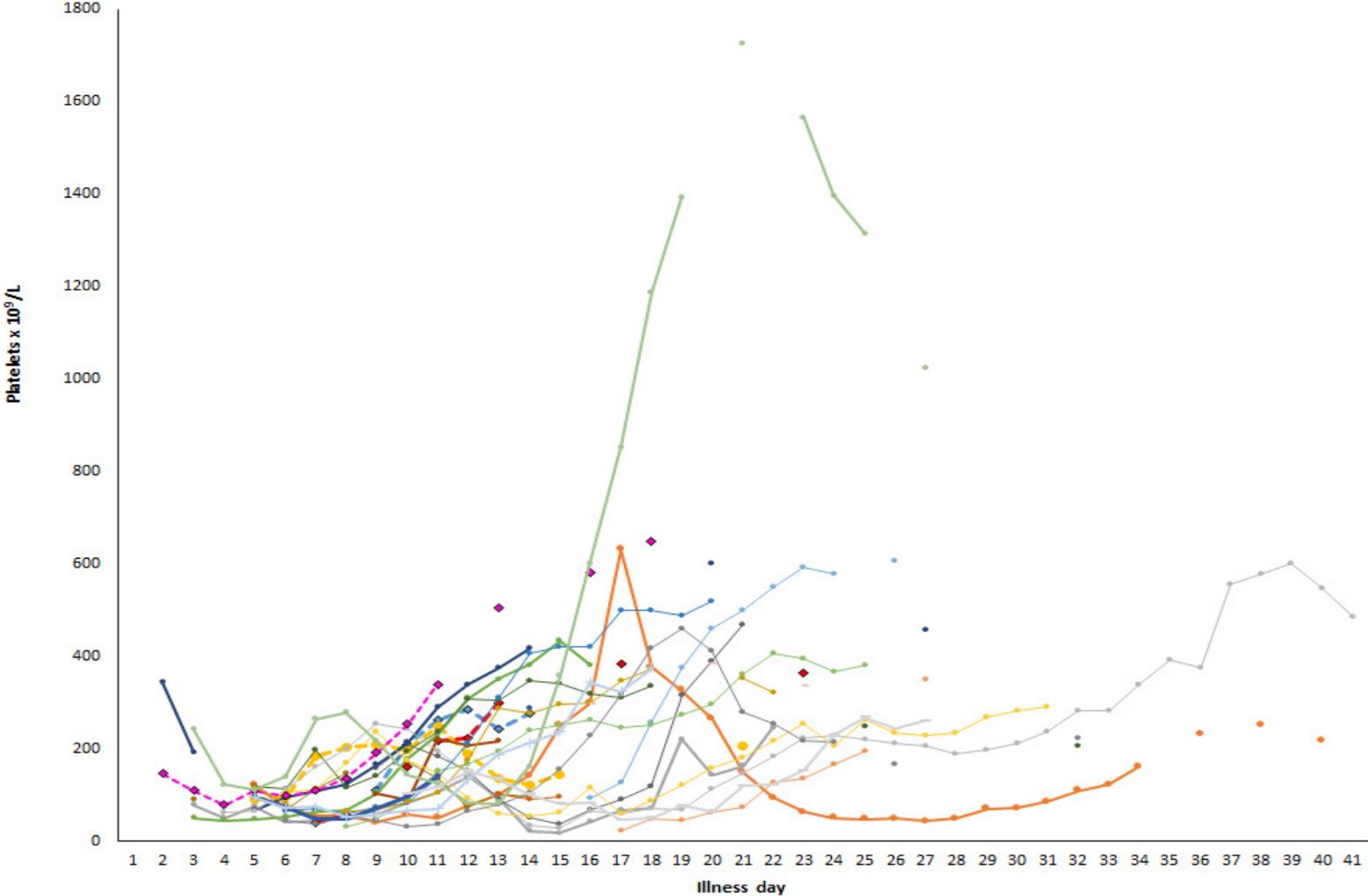
Fatal cases are denoted by diamond markers and dotted lines.

Figure S4. Daily hemoglobin levels for 27 Ebola Virus Disease patients hospitalized in Europe or the U.S.



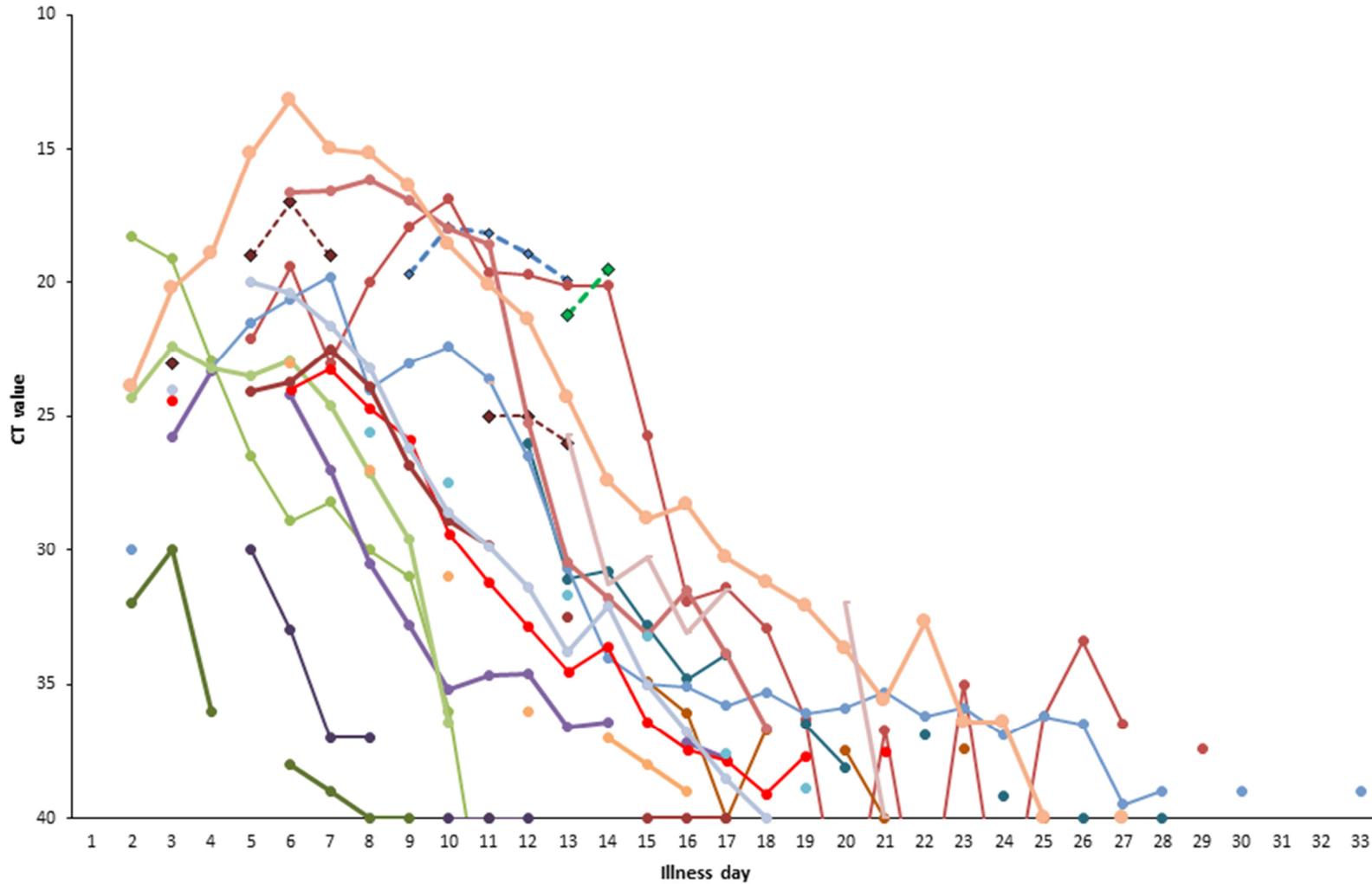
Fatal cases are denoted by diamond markers and dotted lines.

Figure S5. Daily platelet counts for 27 Ebola Virus Disease patients hospitalized in Europe or the U.S.



Fatal cases are denoted by diamond markers and dotted lines.

Figure S7. Daily viral load, Ct values*, for 20 Ebola Virus Disease patients hospitalized in Europe or the U.S.



*Ct values of <40 were considered positive, and ≥ 40 were considered negative.
Fatal cases are denoted by diamond markers and dotted lines.

Table S1. Demographics and Timing by Outcome

	Overall (n= 27)	Medically evacuated (n=20)	Survivors (n=22, 81%)	Fatal cases (n=5, 18.5%)	p-value, survivors vs fatal cases
Median age (range), years	36 (25-75)	36.5 (25-75)	34.5 (25-59)	56 (42- 75)	0.0116
Male, n (%)	19 (70%)	16 (80%)	14 (64%)	5 (100%)	0.11
Comorbidities*	9 (35%)	8 (42%)	6 (27%)	3 (75%)	0.10
Healthcare worker	22 (81%)	15 (79%)	18 (82%)	4 (80%)	1.00
Worked in an ETU in W Africa	17 (63%)	14 (70%)	15 (68%)	2 (40%)	0.33
Medically evacuated	20 (74%)	-	16 (73%)	4 (80%)	1.00
Median (range) days from illness onset to EVD diagnosis	3 (1-9)	3 (1-9)	3 (1-9)	5 (3-7)	0.07
Median (range) days from illness onset to initial hospital admission**	4 (0-15)	4 (0-15)	3.5 (0-15)	5 (4-7)	0.0209
Median duration in days (range) of hospitalization in U.S. or Europe	16 (2-40)	15.5 (2-40)	20 (10-40)	7 (2-11)	0.0149
Median days (range) from illness onset to death/ discharge	23 (11-48)	22.5 (11-46)	28 (14-48)	14 (11-15)	0.0149
Median days (range) from illness onset until medical evacuation		6.5 (4-15)	6 (4-15)	8.5 (7-12)	0.0293

*Comorbidities included cardiac disease, hepatic disease, gastritis/ GERD, asthma, epilepsy, psoriasis, and eczema. In one patient, comorbidities were unknown.

**For 4 imported cases, the median time from illness onset to admission in the U.S. or Europe was 2 days (range 1-4); for 3 secondary cases, the median time from illness onset to admission in the U.S. or Europe was 4 days (range 1-8 days). For imported and secondary cases, the initial hospitalization refers to a hospital in the U.S. or Europe. For most medically evacuated patients, the initial hospital admission was in West Africa – however, a small number of medically evacuated patients were not admitted to a hospital in West Africa before medical evacuation.

Table S2. Laboratory values on admission and most extreme value during hospitalization in the U.S. or Europe

	On admission	Most extreme value during hospitalization						Normal values
	Number tested	Median	Range		Number tested	Median of most abnormal value	Range	
Sodium(mEq/L)	27	136	125-147	Minimum	27	131	119-139	135-145
Potassium (mEq/L)	27	3.6	2.2-4.8	Minimum	27	3.2	1.9-3.6	3.5-5
Chloride (mEq/L)	22	101.5	37-114	Minimum	21	97	91-115	95-105
Bicarbonate (mEq/L)	21	23	9-32.7	Minimum	21	19.2	6.6-25	22-28
Creatinine (mg/dL)	27	1	0.59-15.2	Maximum	27	1.12	0.60-15.2	0.8-1.3
Blood Urea Nitrogen (BUN) (mg/dL)	27	10	2-96	Maximum	27	18.2	6-123	8-21
Glucose (mg/dL)	26 0	94.5	56-279	Minimum	27	78	35-114	65-110
				Maximum	27	154	86-357	
Calcium (mg/dL)	18	5.65	0.9-9.5	Minimum	20	7.12	3.84-8.4	2-2.6
Ionized calcium (mg/dL)	16	4.48	1.9-8.5	Minimum	21	3.96	0.86-7.32	1.03-1.23
Magnesium (mEq/L)	10	0.88	0.3-3	Minimum	17	1.2	0.36-2.5	1.5-2
Albumin (g/dL)	25	3	1.7-4.6	Minimum	25	2.2	1.3-3.4	35-50
Aspartate Aminotransferase (AST) (U/L)*	26	330.5	20-1602	Maximum	25	960	107-2000	5-30
Alanine Aminotransferase (ALT) (U/L)*	26	135.5	15-399	Maximum	27	289	97-892	5-30
Total bilirubin (mg/dL)	22	0.67	0.1-8.6	Maximum	26	1.6	0.5-9	0.3-1.9
Creatinine kinase (CK) (U/L)	14	466	44-4300	Maximum	18	1007.5	44-7860	25-200
Lactate (mmol/L)	16	1.52	0.9-2.3	Maximum	22	2.8	0.7-23.9	0.5-1
White Blood Cells (WBC) ($\times 10^9/L$) [†]	26	5.2	1-4000	Minimum	27	3.6	0.8-11.4	4-10
	0	0	-	Maximum	27	17.9	5.1-51	
Absolute lymphocyte count ($\times 10^9/L$)	23	1.1	0.5-1000	Minimum	23	0.7	0-6.6	1-4
Absolute neutrophil count ($\times 10^9/L$)	23	3.8	0.1-2800	Minimum	23	2.3	0.1-15.3	2-8
Hemoglobin (g/dL)	27	13.6	8.2-20.1	Minimum	27	10.5	7.1-16.9	12-17
Hematocrit (%)	26	41.4	33.7-55.2	Minimum	26	30.55	21.1-47.1	36-52
Platelets ($\times 10^9/L$) [‡]	26	103	24-343	Minimum	27	52	18-298	150-400
				Maximum	27	383	103-1726	
INR	19	1.2	1-2	Maximum	21	1.49	1-10	0.9-1.2
PT (seconds)	13	15	9.6-44.6	Maximum	14	15.7	11.6-51	11-14
PTT (seconds)	12	50.85	28-170	Maximum	13	58.5	29.6-217	20-40
D-dimer (ng/mL) [§]	4	0	0-33,000	Maximum	6	9,825	1,580-38,000	<500
C- reactive protein (mg/L)	6	25	5-96					

**AST peaked on day 9 (range 5-15), ALT peaked on day 9 (range 5-22)*

†WBC was lowest on a median of day 6.5 (2-31), highest on a median of day 13 (11-24)

‡Platelets peaked on median day 16 (3-33)

£Several labs reported DD to a maximum of 20,000ng/ml, thus the true median maximum value may be higher than reported

Table S3. Treatments administered during hospitalization in U.S. or Europe among 27 patients

	Number receiving treatment	%	Comments
Intravenous fluids*	26	96%	Median 4000ml/day (range 0-13,734 ml)
Total Parenteral Nutrition	15	56%	
Antiemetics	22	82%	Ondansetron (16), metoclopramide (14); 8 patients received both ondansetron and metoclopramide. 2 patients received dimenhydrinate. 1 patient received each of: pantoprazole, compazine, droperidol, phenergan, and promethazine.
Antidiarrheals	7	26%	4 received loperamide, 1 received diphenoxylate/atropine, and 2 received racecadotril
Anticonvulsants	2	7%	carbamazepine and levetiracetam
Anxiolytics	13	50%	1 received haloperidol, the rest received benzodiazepines
Whole blood or packed RBCs (non-convalescent)	4	15%	
Fresh Frozen Plasma	6	22%	
Platelets	5	19%	
IVIG	0	0%	
Antibiotics	22	81%	Patients received a median of 2 antibiotics (range 0-7), including 3 rd generation cephalosporin (12 patients), carbapenems (11), metronidazole (5), vancomycin (5, 4 IV and 1 PO), fluoroquinolones (6), piperacillin/ tazobactm (3), linezolid (2), macrolides (2), doxycycline (1), teicoplanin (1), gentamicin (1), ceftaroline (1), colisitn (1), tigecycline (1), amoxicillin/clavulanate (1)
Antifungals	8	31%	2 received fluconazole, 2 received anidulafungin (one also received fluconazole), 3 received micafungin,, one received topical lotrimin, one received oral nystatin
Antimalarials**	8	30%	Atovaquone/proguanil (2 for prophylaxis) (5), artesunate (1), mefloquine prophylaxis (1), doxycycline (1) (to a patient who also received atovaquone/proguanil), cloroquine + primaquine (1)
Corticosteroids	8	30%	Hydrocortisone (5), methylprednisone (4), dexamethasone (1)
Analgesics	20	80%	Acetaminophen 22 (88%), NSAID (not ibuprofen) 4 (16%)
Sedation	13	48%	Propofol (4), haloperidol (3), midazolam (2), dexmedetomidine (2), quetiapine fumarate (2), diazepam, zolpidem, zopiclon, fentanyl, ketamine, oxycontin
Narcotics	14	52%	
Paralytics	3	11%	Rocuronium (2), Vecuronium + cisatracurium (1)
Albumin	7	26%	
Potassium (IV or PO)	27	100%	Intravenous potassium 25 (93%), Oral potassium 9 (33%)
Calcium	15	56%	
Magnesium	17	63%	

*One patient who was managed with oral rehydration after medical evacuation had received IV fluids in West Africa.

**Overall, 17 patients received any antimalarial. 14 patients received antimalarials in West Africa (4 received prophylaxis while 10 received treatment). Of the 8 patients who received antimalarials in the US or Europe, 5 had

received either prophylaxis (3) or treatment (2) in West Africa. Overall, 5 patients received prophylaxis, 10 received treatment or presumptive treatment, and 2 received both prophylaxis and treatment.

Table S4. Results of Ebola virus testing of different clinical specimens from Ebola Virus Disease patients by RT-PCR during hospitalization in Europe or the U.S.

Body site	Positive / Patients Tested (%)	Illness day of first negative RT-PCR result		
		n	Median	Range
Saliva	8/12 (67%)	8	18	(9-24)
Sweat*	6/13 (46%)	4	27	(24-32)
Stool	7/10 (70%)	5	18	(10-28)
Rectal swab	3/5 (60%)	3	15	(10-15)
Skin swab	5/9 (56%)	3	24	(11-32)
Vaginal swab [‡]	2/6 (33%)	3	24	(19-30)
Semen**	5/6 (83%)			

*inconclusive RT-PCR result from 1 sweat specimen

[‡]N=8 women

**inconclusive RT-PCR results from 1 semen specimen, n = 19

Table S5. Outcomes among survivors (N=22)

	n	%
Discharged home	20	91%
Discharged to rehabilitation facility	2	9%
Status at discharge		
Weakness	18	82%
Weight loss	17	77%
Abnormal lab results*	18	82%
Anemia	13	59%
Supplemental oxygen	0	0%
Dialysis	0	0%

*10 patients were reported to have persistently elevated hepatic function tests, 6 patients with abnormal platelets, 4 with abnormal creatinine, 3 with abnormal WBC, 4 with hypoalbuminemia, 2 with abnormal GGT, 1 with each of: elevated creatinine kinase, hypothyroidism, alkaline phosphatase, phosphate, and C-reactive protein.

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