1 Antiviral Therapeutics for the Treatment of Ebola Virus Infection

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Abstract:

There have been significant developments in Ebola virus therapeutics. While the efficacy of several products was evaluated in the recent West Africa outbreak, a licensed treatment for EBOV disease remains elusive. Factors that negatively impacted the execution of clinical trials included an overall lack of world readiness to conduct clinical trials in an outbreak setting, ethical concerns limiting implementation of the randomized controlled trials in an outbreak setting, and a decline in case numbers by the time resources were mobilized to conduct clinical trials. We summarize relevant therapeutics that underwent clinical trials during the West Africa outbreak and highlight promising candidates under advanced development.

Introduction:

According to the last World Health Organization (WHO) situation report there have been 28,616 total cases and 11,310 deaths during the West Africa Ebola virus outbreak [1]. The recent outbreak of EBOV in West Africa was caused by a new variant of EBOV that has been named Makona [2]. Prior to the recent outbreak, there was no EBOV therapeutic in clinical trials. Although there have been tremendous efforts to advance EBOV therapeutics and to conduct clinical trials in an outbreak setting, there remains no licensed treatment for EBOV disease. The cause of this outcome was multifactorial and included an overall lack of world readiness to conduct clinical trials in an outbreak setting. As a result, by the time clinical trials could be executed case counts were low, which compromised the statistical power of the studies. Additionally, ethical concerns limited implementation of the gold standard placebo-controlled, randomized trial in the outbreak setting.

The goal of this review article is to summarize relevant therapeutics that underwent clinical trials during the West Africa outbreak and to highlight promising candidates that may be available for future outbreaks (Table 1). Numerous repurposed drugs were also considered during the recent EBOV outbreak such as amodiaquine, amiodarone, lamivudine, atorvastatin, irbesartan, and sertraline. Utilization of these drugs as EBOV therapeutics is beyond the scope of this work and is covered in other sources [3,4].

NUCLEIC-ACID BASED INHIBITORS

Nucleic-acid based inhibitors, antisense phosphorodiamidate morpholino oligomers (PMOs) and small-interfering RNAs (siRNAs), had shown promise as EBOV therapeutics in nonclinical studies prior to the West Africa EBOV Outbreak. The development and chemical

modification of siRNAs and PMOs have been detailed in other sources [5-7]. A key concern with these products is that they are sequence specific and may be ineffective for new outbreak variants.

A combination PMO, AVI-6002 (AV-7537 and AV-7539), which targets Ebola virus VP24 and VP35 respectively demonstrated efficacy in non-human primate (NHP) studies, and safety in phase 1 single-ascending-dose studies [8]. In the phase 1 studies, the primary adverse events were non-dose dependent headache and gastrointestinal disorders (nausea, diarrhea, etc.) [8]. NHP studies would eventually reveal that VP24 (AVI-7537) targeting was primarily responsible for the observed antiviral activity [9]. There has been no further development of AVI-6002 or AVI-7537, and product support has been withdrawn by the sponsor.

There have been progressions of anti-EBOV siRNA products by Arbutus BioPharma (formerly Tekmira) that have demonstrated efficacy in nonclinical NHP studies [10,11]. While most antiviral research prior to this most recent outbreak was based on the 1995 EBOV-Kikwit variant, gene sequencing EBOV-Makona revealed mismatches in siRNA targets and a need for a modified siRNA cocktail to treat this variant [11]. This came in the form of siEbola-3, also known as TKM-130803, which proved efficacious against the EBOV-Makona in non-human primates [11]. An open-label, non-randomized, single-arm trial of TKM-130803 at 0.3 mg/kg by intravenous infusion once daily for up to 7 d was conducted in Sierra Leone during the West Africa EBOV outbreak [12]. Unfortunately, after 14 adults with EBOV had received TKM-130803, the pre-specified futility boundary was reached, indicating a probability of survival to day 14 of ≤ 0.55 , and the trial was terminated [12]. However, no further advances have been reported since publication of their clinical trial results.

NUCLEOSIDE/NUCLEOTIDE VIRAL POLYMERASE INHIBITORS

Nucleoside and nucleotide antivirals have thus far been the most successful class of antivirals given their success in treating HIV and herpes viruses. There are four nucleoside/nucleotide analogues that merit discussion as anti-EBOV therapeutics: BCX4430, brincidofovir, favipiravir, and GS-5734.

BCX4430 is an adenosine nucleoside analogue currently under investigation as a treatment for a number of viral infections including EBOV [13]. It inhibits RNA synthesis by adding a highly selective monophosphate nucleotide to the nascent RNA chain, interrupting elongation [13,14]. Using regimens developed for Marburg virus indications, administration of BCX4430 to cynomolgus macaques resulted in a decreased time to death when administered 48 hours after EBOV challenge [13]. Using increased doses, up to 100% survival of rhesus monkeys was observed when BCX4430 was administered 30-60 minutes after EBOV challenge [13,14]. Phase 1 clinical trials for BCX4430, dosed intramuscularly are being conducted with plans for intravenous studies in the future [13].

Brincidofovir, a conjugate of cidofovir, was originally studied as a treatment for double-stranded DNA viruses [15]. Its mechanism of action is not well characterized for RNA viruses, but *in vitro* studies with EBOV have demonstrated a relationship between the anti-viral properties and the lipid nucleotide conjugate [15]. As the West Africa outbreak progressed, brincidofovir was found to have *in vitro* activity against EBOV. Because brincidofovir was in advanced trials for other viral indications, it was thought it could be an effective EBOV therapeutic. An efficacy trial was commenced in West Africa, but in January 2015, the trial was ceased due to low enrollment [15]. It was administered to three patients in the United States, who recovered, but the drug's relationship to their survival is not easily established due to other

interventions conducted during the care of these patients [16]. The rapid metabolism of brincidofovir in non-human primates creates a barrier to an effective development of brincidofovir under the Animal Rule [15]. Overall, these difficulties preclude further investigation of this drug for EBOV therapy, and the product sponsor has withdrawn its support of brincidofovir for an EBOV indication [17].

Favipiravir is a nucleotide analogue that acts as a pseudo purine, had completed advanced clinical trials for influenza, and was an attractive candidate for EBOV therapy during the West Africa Outbreak as it had demonstrated efficacy in mouse models of EBOV infection [18,19]. The JIKI trial, a historically controlled, multisite, single arm clinical trial to evaluate the efficacy of oral favipiravir in EBOV infected patients was conducted in Guinea [20]. In addition to favipiravir, patients in the trial received supportive care (oral or intravenous rehydration, electrolyte correction, empiric antimalarial and antibacterial therapies, analgesics, and antiemetic drugs) [20]. The data for 99 adults and adolescents enrolled was analyzed, but due to the study design, no conclusions on efficacy were able to be drawn [20]. However, the data suggests that in patients with medium to high Ebola viremia ($CT > 20$), favipiravir therapy could have efficacy compared to those with very high viremias ($CT < 20$) [20].

GS-5734 is the newest polymerase inhibitor being evaluated as a therapeutic for EBOV. It is a small-molecule monophosphoramidate prodrug of an adenosine analogue [21]. In animal-model pharmacokinetic studies, GS-5734 was rapidly converted to its pharmacologically active triphosphate form and was persistent in the intracellular compartment. [21]. In an NHP model of EBOV infection, administration of a 10 mg/kg loading dose followed by 3 mg/kg daily or 10 mg/kg daily maintenance doses, beginning 3 days after EBOV challenge, resulted in 100% survival [21]. In addition, in NHPs the drug has been found to distribute into the testes,

epididymis, eyes, and brain within 4 h of administration [21]. As a result, GS-5734 may also be of efficacy in post-Ebola syndrome and eradication of persistent viral replication in the genital tract. Another advantage of GS-5734 is rapid distribution to cells of the mononuclear line, with rapid formation of the active metabolite and maintenance of levels calculated as sufficient for viral inhibition for approximately 24 h [21]. Given that the initial target cells for EBOV infection are cells of the mononuclear line, GS-5734 may also be valuable for post-exposure prophylaxis of high-risk exposures. The drug was used in the case of a nurse who suffered an EBOV relapse causing meningoencephalitis and in an infant in Guinea [22,23]. Both individuals survived infection, however it is difficult to gauge the impact of the drug in individual case reports. Intravenous GS-5734 is currently undergoing human phase 1 studies [21,24].

IMMUNOTHERAPEUTICS

Clinical trials on three immunotherapeutics were conducted during the West Africa EBOV outbreak: convalescent plasma, ZMapp, and Interferon- β (INF- β). Convalescent plasma received a significant amount of attention, with three separate clinical trials; however to date results of only one study have been published [25]. This study was non-randomized, historically controlled, and patients received two consecutive transfusions of ABO-compatible convalescent plasma [26]. Eighty-four patients were enrolled in the study and there was no significant difference in mortality between those treated with convalescent plasma and the historical controls [26]. One criticism of this study was that titers of neutralizing antibodies in the plasma were not determined prior to transfusion. Lessons learned from pre-outbreak human and *in vivo* studies need to be applied to future studies: antibody titers in human convalescent plasma tend to be low, frequent dosing is needed to maintain antibody titers, survival can correlate with anti-

EBOV IgG titers, and titer of different plasma pools is variable between batches [3]. Another recent study suggests that in patients recovering from EBOV infection, neutralizing antibody titers increase from 2 to 9 months [27]. As a result, the patients who received convalescent plasma as therapy likely received variable neutralizing antibody concentrations. These issues could be overcome with hyperimmune plasma (increased potency) as illustrated in an NHP study [28]. However, this would introduce the logistical challenge of producing adequate quantities and as a result would require pre-outbreak stockpiling. In addition, if there are significant antigenic variations between outbreaks, the efficacy of stockpiled plasma may be diminished.

A potential solution to convalescent or hyperimmune plasma are monoclonal antibodies which can be manufactured in large scale, engineered to improve therapeutic efficacy and can be formulated in cocktails of more than one antibody to decrease the risk of treatment failure that may occur with genetic changes. During the West Africa EBOV outbreak, the monoclonal antibody cocktail ZMapp (mixture of antibodies from MB-003/ZMAb developed against the Kikwit variant) was used on a compassionate-use basis in numerous patients and in a Phase 2 clinical trial. ZMapp had previously displayed significant efficacy in NHP models of EBOV infection [29]. Fortunately, the epitopes of the outbreak strain, EBOV-Makona were not mutated, and a decrease in ZMapp efficacy was not expected [29]. ZMapp was evaluated in the PREVAILII study, which was the only randomized, controlled trial to be conducted during the West Africa outbreak. The study had a unique adaptive design and patients were randomized to receive either optimized standard of care or optimized standard of care plus three IV infusions of ZMapp three days apart [30,31]. Seventy-two patients were enrolled, but there was no statistically significant mortality benefit conferred by ZMapp in the study [30]. It is possible that efficacy was not demonstrated as the study was underpowered, or the dosing regimen was not

214 optimized. New and interesting studies continue to be released on newly discovered pan-EBOV
215 antibodies, and the addition of a monoclonal to the ZMapp cocktail to broaden its EBOV
216 spectrum [32,33].

217 Finally, an INF- β efficacy trial was conducted in Guinea, however results are not
218 currently available in the literature [25]. This therapy was attempted as INF- β production is
219 suppressed in EBOV infection, and INF- β therapy in NHP EBOV has been shown to extend
220 time to death [34,35].

221 222 **CONCLUSIONS**

223 Despite the recent occurrence of the largest EBOV outbreak in history, there remains no
224 licensed treatment for EBOV to date. None of clinical trials conducted during the outbreak were
225 able to statistically demonstrate efficacy and only one randomized controlled trial was
226 conducted. The failure to generate key efficacy data were primarily a consequence of restricted
227 study designs guided by legitimate ethical concerns and a decline in case numbers by the time
228 resources could be mobilized to conduct clinical trials. Planning for the next outbreak needs to
229 take place to develop capabilities to facilitate more efficient conduct of clinical trials in an
230 outbreak setting in concert with at-risk nations. This planning should also take into
231 consideration of study design early with the host nation, and the need for creative study designs.
232 For example, the adaptive model employed by PREVAILII could mitigate ethical concerns and
233 still enable conduct of a randomized controlled trial.

234 In addition, there are a number of important concepts learned about EBOV disease that
235 should impact therapeutics development. A post-EVD syndrome has been described and is
236 associated with EBOV persistence in privileged sites such as the eyes and genital tract. As a

result of persistence in the genital tract, EBOV can now also be considered a sexually transmitted infection. Therapeutics programs should thus consider the tissue penetration of drugs being considered into relevant privileged sites to potentially treat post-infectious EBOV syndrome and persistent infection. It is important to explore combination therapies for EBOV given that most patients treated in Western hospitals, which exhibited uncharacteristically low mortality rates, received more than one investigational therapeutic in addition to aggressive supportive care.

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References:

1. World Health Organization. *Ebola Virus Situation report*. Available at: http://apps.who.int/iris/bitstream/10665/208883/1/ebolasitrep_10Jun2016_eng.pdf?ua=1. (Accessed on June 25, 2016).
2. Kuhn JH, Andersen KG, Baize S, Bao Y, Bavari S, Berthet N, Blinkova O, Brister JR, Clawson AN, Fair J, et al.: **Nomenclature- and database-compatible names for the two Ebola virus variants that emerged in Guinea and the Democratic Republic of the Congo in 2014**. *Viruses* 2014, **6**:4760-4799.
3. Cardile A, Mayers D, Bavari S: **Emerging options in development for treatment of filovirus infections**. *DRUGS OF THE FUTURE* 2015, **40**:727-738.
4. Mendoza EJ, Qiu X, Kobinger GP: **Progression of Ebola Therapeutics During the 2014-2015 Outbreak**. *Trends Mol Med* 2016, **22**:164-173.
5. Friedrich BM, Trefry JC, Biggins JE, Hensley LE, Honko AN, Smith DR, Olinger GG: **Potential vaccines and post-exposure treatments for filovirus infections**. *Viruses* 2012, **4**:1619-1650.
6. Kole R, Krainer AR, Altman S: **RNA therapeutics: beyond RNA interference and antisense oligonucleotides**. *Nat Rev Drug Discov* 2012, **11**:125-140.
7. Spurgers KB, Sharkey CM, Warfield KL, Bavari S: **Oligonucleotide antiviral therapeutics: antisense and RNA interference for highly pathogenic RNA viruses**. *Antiviral Res* 2008, **78**:26-36.
8. Heald AE, Iversen PL, Saoud JB, Sazani P, Charleston JS, Axtelle T, Wong M, Smith WB, Vutikullird A, Kaye E: **Safety and pharmacokinetic profiles of phosphorodiamidate morpholino oligomers with activity against ebola virus and marburg virus: results of two single-ascending-dose studies**. *Antimicrob Agents Chemother* 2014, **58**:6639-6647.
9. Warren TK, Whitehouse CA, Wells J, Welch L, Heald AE, Charleston JS, Sazani P, Reid SP, Iversen PL, Bavari S: **A single phosphorodiamidate morpholino oligomer targeting VP24 protects rhesus monkeys against lethal Ebola virus infection**. *MBio* 2015, **6**.

10. Geisbert TW, Hensley LE, Kagan E, Yu EZ, Geisbert JB, Daddario-DiCaprio K, Fritz EA, Jahrling PB, McClintock K, Phelps JR, et al.: **Postexposure protection of guinea pigs against a lethal ebola virus challenge is conferred by RNA interference.** *J Infect Dis* 2006, **193**:1650-1657.
11. Thi EP, Mire CE, Lee AC, Geisbert JB, Zhou JZ, Agans KN, Snead NM, Deer DJ, Barnard TR, Fenton KA, et al.: **Lipid nanoparticle siRNA treatment of Ebola-virus-Makona-infected nonhuman primates.** *Nature* 2015, **521**:362-365.
12. Dunning J, Sahr F, Rojek A, Gannon F, Carson G, Idriss B, Massaquoi T, Gandhi R, Joseph S, Osman HK, et al.: **Experimental Treatment of Ebola Virus Disease with TKM-130803: A Single-Arm Phase 2 Clinical Trial.** *PLoS Med* 2016, **13**:e1001997.*
13. Taylor R, Kotian P, Warren T, Panchal R, Bavari S, Julander J, Dobo S, Rose A, El-Kattan Y, Taubenheim B, et al.: **BCX4430 - A broad-spectrum antiviral adenosine nucleoside analog under development for the treatment of Ebola virus disease.** *J Infect Public Health* 2016, **9**:220-226.
14. Warren TK, Wells J, Panchal RG, Stuthman KS, Garza NL, Van Tongeren SA, Dong L, Retterer CJ, Eaton BP, Pegoraro G, et al.: **Protection against filovirus diseases by a novel broad-spectrum nucleoside analogue BCX4430.** *Nature* 2014, **508**:402-405.
15. McMullan LK, Flint M, Dyall J, Albarino C, Olinger GG, Foster S, Sethna P, Hensley LE, Nichol ST, Lanier ER, et al.: **The lipid moiety of brincidofovir is required for in vitro antiviral activity against Ebola virus.** *Antiviral Res* 2016, **125**:71-78.
16. Florescu DF, Kalil AC, Hewlett AL, Schuh AJ, Stroher U, Uyeki TM, Smith PW: **Administration of Brincidofovir and Convalescent Plasma in a Patient with Ebola Virus Disease.** *Clin Infect Dis* 2015.
17. Chimerix, inc. *Brincidofovir Will Not Be Considered in Further Clinical Trials in Ebola Virus Disease.* Available at: <http://ir.chimerix.com/releasedetail.cfm?releaseid=893927>. (Accessed on: October 11, 2015).
18. Oestereich L, Rieger T, Neumann M, Bernreuther C, Lehmann M, Krasemann S, Wurr S, Emmerich P, de Lamballerie X, Olschlager S, et al.: **Evaluation of antiviral efficacy of ribavirin, arbidol, and T-705 (favipiravir) in a mouse model for Crimean-Congo hemorrhagic fever.** *PLoS Negl Trop Dis* 2014, **8**:e2804.
19. Smither SJ, Eastaugh LS, Steward JA, Nelson M, Lenk RP, Lever MS: **Post-exposure efficacy of oral T-705 (Favipiravir) against inhalational Ebola virus infection in a mouse model.** *Antiviral Res* 2014, **104**:153-155.
20. Sissoko D, Laouenan C, Folkesson E, M'Lebing AB, Beavogui AH, Baize S, Camara AM, Maes P, Shepherd S, Danel C, et al.: **Experimental Treatment with Favipiravir for Ebola Virus Disease (the JIKI Trial): A Historically Controlled, Single-Arm Proof-of-Concept Trial in Guinea.** *PLoS Med* 2016, **13**:e1001967.*
21. Warren TK, Jordan R, Lo MK, Ray AS, Mackman RL, Soloveva V, Siegel D, Perron M, Bannister R, Hui HC, et al.: **Therapeutic efficacy of the small molecule GS-5734 against Ebola virus in rhesus monkeys.** *Nature* 2016.
22. Farge E. 2015. *Guinea's last Ebola case, a baby girl, leaves hospital.* Available at: <http://www.reuters.com/article/us-health-ebola-guinea-idUSKBN0TH0PB20151128>. Accessed on March 5, 2016.
23. Jacobs M, Rodger A, Bell DJ, Bhagani S, Cropley I, Filipe A, Gifford RJ, Hopkins S, Hughes J, Jabeen F, et al.: **Late Ebola virus relapse causing meningoencephalitis: a case report.** *Lancet* 2016.
24. Gilead. *Gilead Pipeline.* Available at: <http://www.gilead.com/research/pipeline>. Accessed on March 5, 2016.
25. Cohen J, Enserink M: **As Ebola epidemic draws to a close, a thin scientific harvest.** *Science* 2016, **351**:12-13.

26. van Griensven J, Edwards T, de Lamballerie X, Semple MG, Gallian P, Baize S, Horby PW, Raoul H, Magassouba N, Antierens A, et al.: **Evaluation of Convalescent Plasma for Ebola Virus Disease in Guinea.** *N Engl J Med* 2016, **374**:33-42.*
27. Luczkowiak J, Arribas JR, Gomez S, Jimenez-Yuste V, de la Calle F, Viejo A, Delgado R: **Specific neutralizing response in plasma from convalescent patients of Ebola Virus Disease against the West Africa Makona variant of Ebola virus.** *Virus Res* 2016, **213**:224-229.
28. Dye JM, Herbert AS, Kuehne AI, Barth JF, Muhammad MA, Zak SE, Ortiz RA, Prugar LI, Pratt WD: **Postexposure antibody prophylaxis protects nonhuman primates from filovirus disease.** *Proc Natl Acad Sci U S A* 2012, **109**:5034-5039.
29. Qiu X, Wong G, Audet J, Bello A, Fernando L, Alimonti JB, Fausther-Bovendo H, Wei H, Aviles J, Hiatt E, et al.: **Reversion of advanced Ebola virus disease in nonhuman primates with ZMapp.** *Nature* 2014, **514**:47-53.
30. Davey R. 2016. *PREVAIL II: A Randomized Controlled Trial of ZMapp™ in Acute Ebola Virus Infection*. Available at: <http://www.croiwebcasts.org/console/player/29572?mediaType=audio&>. Accessed on March 10, 2016*.
31. Dodd LE, Proschan MA, Neuhaus J, Koopmeiners JS, Neaton J, Beigel JD, Barrett K, Lane HC, Davey RT, Jr.: **Design of a randomized controlled-trial for Ebola virus disease medical countermeasures: PREVAIL II, the Ebola MCM study.** *J Infect Dis* 2016.*
32. Furuyama W, Marzi A, Nanbo A, Haddock E, Maruyama J, Miyamoto H, Igarashi M, Yoshida R, Noyori O, Feldmann H, et al.: **Discovery of an antibody for pan-ebolavirus therapy.** *Sci Rep* 2016, **6**:20514.
33. Howell KA, Qiu X, Brannan JM, Bryan C, Davidson E, Holtsberg FW, Wec AZ, Shulenin S, Biggins JE, Douglas R, et al.: **Antibody Treatment of Ebola and Sudan Virus Infection via a Uniquely Exposed Epitope within the Glycoprotein Receptor-Binding Site.** *Cell Rep* 2016, **15**:1514-1526.
34. Yen BC, Basler CF: **Effects of Filovirus Interferon Antagonists on Responses of Human Monocyte-Derived Dendritic Cells to RNA Virus Infection.** *J Virol* 2016, **90**:5108-5118.
35. Smith LM, Hensley LE, Geisbert TW, Johnson J, Stossel A, Honko A, Yen JY, Geisbert J, Paragas J, Fritz E, et al.: **Interferon-beta therapy prolongs survival in rhesus macaque models of Ebola and Marburg hemorrhagic fever.** *J Infect Dis* 2013, **208**:310-318.

Annotated Reference Descriptions:

References 12,20,26: These articles describe efficacy studies against Ebola virus conducted during the West Africa outbreak that are available to date in the peer reviewed literature.

Reference 30: PREVAILII study that evaluated the efficacy of ZMapp is described at the 2016 Conference on Retroviruses and Opportunistic Infections (CROI).

Reference 31: Describes the design of the PREVAILII study which evaluated ZMapp.

Table 1. Ebola virus therapeutics in advanced development.

<i>Therapeutic</i>	<i>Mechanism</i>	<i>Efficacy in NHP Studies</i>	<i>Human Safety & Pharmacokinetics Studies Complete or Pending</i>	<i>Human Efficacy Studies Conducted</i>	<i>Advantages</i>	<i>Disadvantages</i>
BCX-4430	Viral RNA Polymerase Inhibition	YES	YES	NO	Currently under phase I clinical trials	Little clinical data available
GS-5734	Viral RNA Polymerase Inhibition	YES	YES	NO	High potency against EBOV; Currently under phase I clinical trials	Little clinical data available
Brincidofovir	Not well characterized for RNA viruses, appears related to lipid nucleotide conjugate	NO	YES	YES; Results unpublished to date	Clinical data for other indications	Difficult to test in established animal models
Favipiravir	Viral RNA Polymerase Inhibition, lethal mutagenesis	None published	YES	YES; No conclusions able to be drawn; possible benefit in those with baseline Ct values ≥ 20	Oral administration; Safety in advanced clinical trials for other indications	Efficacy may be viral load dependent; Need for dose optimization
AVI-6002 & AVI 7537	Morpholino oligomers that inhibit translation via steric hindrance	YES	YES	NO	Completed phase I clinical trials	EBOV Zaire specific
TKM 130803	Double-stranded oligonucleotides that cause RNA interference (RNAi), silencing gene expression via mRNA degradation	YES	YES	YES; Trial terminated for futility	Completed phase I clinical trials	EBOV Zaire specific

Convalescent Plasma	Viral neutralization, antigen clearance	Conflicting	N/A	YES; No improvement in survival	Inexpensive, readily available in a large outbreak setting	Need ABO- compatibility; Need to determine optimal collection time from donors and if antibody titers correlate with efficacy
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