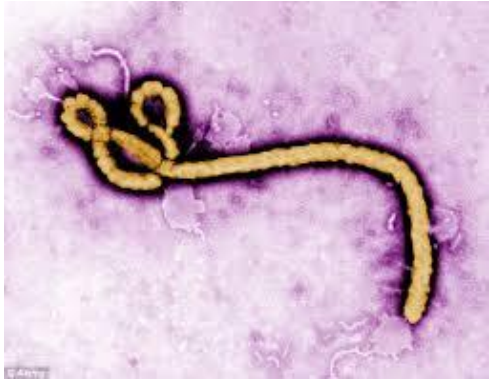


Emergency evaluation of convalescent plasma (CP) for Ebola Viral Disease (EVD) in Guinea

Johan van Griensven on behalf of the **Ebola_Tx consortium**

WHO priorization & guidance

Use of Convalescent Whole Blood or Plasma Collected from Patients Recovered from Ebola Virus Disease for Transfusion, as an Empirical Treatment during Outbreaks

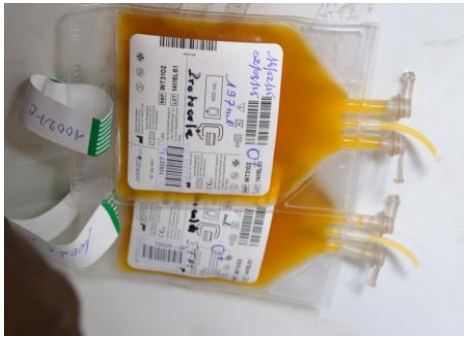
Interim Guidance for National Health Authorities and Blood Transfusion Services

Version 1.0 September 2014

World Health Organization

Methodology (1)

- Main objective: To assess if CP + SC improves the 14 day survival of patients, compared to SC alone; 20% absolute decrease in mortality
- Study intervention
  - Total 400-500ml (2 x 200-250ml units of CP – 2 donors)
    - Pathogen inactivation
  - As per WHO guidance
    - No EBOV titre (neutralizing activity) results required before use
    - Conduct retrospectively/during implementation

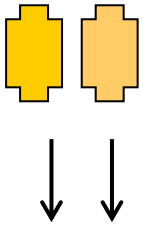


Methodology (2): Design

Non-randomized comparative study

Allocation determined by availability of ABO compatible CP

EVD (all ages, pregnancy)



14 day survival

Adverse reactions

CP+SC

SC

Exclusion Criteria:
Contra-indication/Futility

Methodology (3): Efficacy analysis

- Primary analysis
  - 14 day survival: CP + supportive care vs supportive care
- Primary analysis population
  - CP given within 2 days – CP group excluding early deaths
  - Excluding early deaths (2 days) in both CP & control group
- Logistic regression
  - Adjusted for pre-defined factors:
    - Age: <5, 5-15, 15-45; 45+
    - CT value: <25; 25-30; >30 (IP Dakar PCR)
  - Imbalances in symptoms/signs

Methodology (4): Sample size

- Sample size (20% absolute difference)
  - 130 patients treated with CP (relatively few SC controls)
- Study start: low case load, enough donors – Protocol amendment:
  - Historical controls
    - 5 months before trial
    - Same time/supportive care guidelines – MSF team
- Trial stopped with 102 patients enrolled
  - 1/5 ratio CP vs controls – power retained

Results (1): Flow chart

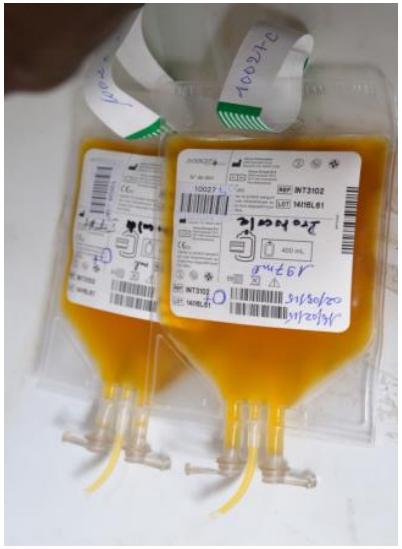
	CP+SC	SC
EVD	114	507
Early deaths	19 (16.7%)	87 (17.1%)
Favipiravir	10	0
Missing data	1	2
Analysis	84	418

Results (2): Baseline characteristics

Variable	CP + SC (n=84)	SC (n=418)	P value
Male sex	36 (42.9)	210 (50.2)	0.25
Age			
< 5 years	5 (5.9)	23 (5.5)	0.79
5-15 years	8 (9.5)	53 (12.7)	
16-44 years	57 (66.7)	258 (61.7)	
45+ years	15 (17.9)	84 (20.1)	
PCR CT value			
<25	21 (25.0)	159 (38.0)	0.05
25.0-29.9	41 (48.8)	183 (43.8)	
≥30	22 (26.2)	76 (18.2)	

Results (3): Safety

- Serious adverse reactions: 0
- Adverse reactions: 8 of 99 CP patients
  - Itch/skin rash: 3
  - Raise in temperature: 3
  - Itch/skin rash & nausea: 1
  - Itch/skin rash & raise in temperature: 1



Results (4): Efficacy

	CP + SC (n=84)	SC (n=418)
Deaths 3-16 days	26 (31.0%)	158 (37.8%)
Crude analysis	Absolute risk difference: -6.9% (95% CI **-17.8** to 4.1)	
Adjusted analysis	Absolute risk difference: -2.6 (95% CI **-13.1** to 8.0)	
CFR / ITT	42.5%	48.5%
	Absolute risk difference: -6.0%	

Conclusions (1)

- CP transfusions safe & acceptable - feasible
- Unselected CP administration 500 ml
  - A small insignificant decrease in mortality (adjusted analysis) in CP group.
  - A pre-specified 20% absolute decrease in mortality excluded (adjusted risk difference -2.6%, 95% CI: -13.1% to 8.0%)
  - Trial powered to detect this 20% difference
- No conclusion beyond this

Conclusions/perspectives (2)

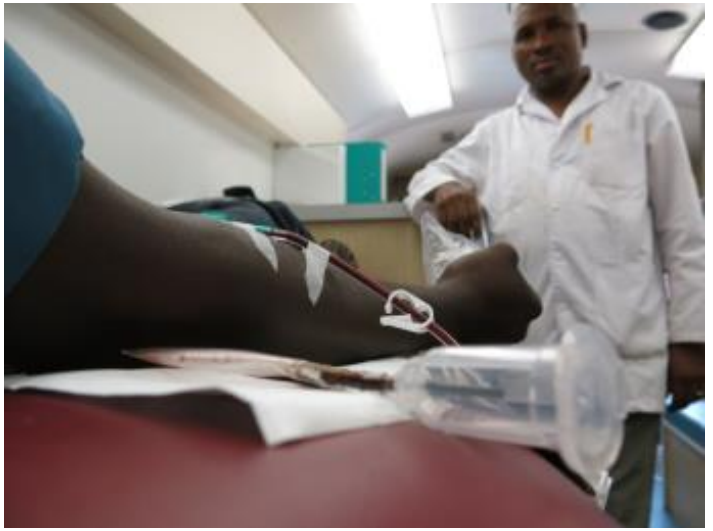
- Level of neutralizing antibodies not yet known
  - Dilution of effect by low antibody donors?
  - Only conclude on use of unselected CP
- Association donor Ab titer with CT change/survival
  - Dose response effect?
- Volume? Frequency?

Study limitations

- Historical controls
- Changes in supportive care?
- Safety:
  - Difficult to differentiate AR & EVD (TRALI)

Acknowledgments

- All partners and stakeholders
- Patients, donors and all health care staff in the field



Consortium

ITM (consortium leader/sponsor)

Methodological aspects

LSHTM

University of Oxford

University of Liverpool

Laboratory

Université Aix-Marseille

Institut Pasteur/INSERM

Blood transfusion

Guinean Transfusion Service

EFS

Belgian Red Cross - Flanders

Laboratoire Ebola – Donka

Maferyniah Center

INRB – Prof Muyembe

Antropologists

MSF - WHO/ISARIC

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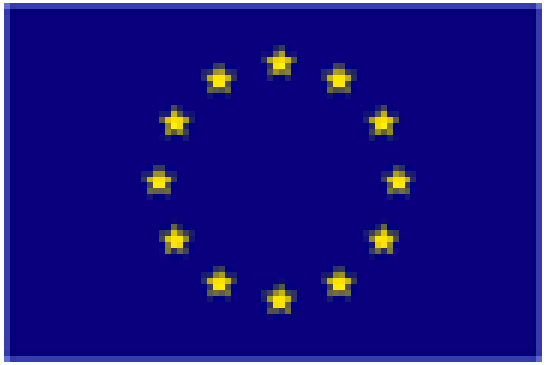

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