Australian Government
Department of Health
Therapeutic Goods Administration

# Development of plasma therapies for emerging infectious diseases

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TGA Health Safety Regulation

# Therapeutic Goods Administration (TGA)

- A part of the Australian Government Department of Health
- Main offices in Canberra – satellite offices in Sydney, Melbourne, Adelaide and Brisbane
- Regulates the safety, quality and efficacy of therapeutic goods in Australia
- Regulates medicines, devices, biologicals and blood
- Operations are primarily cost recovered (98%) industry pays fees for making applications and annual charges for products they are responsible for

# Overview

- Background
- History of plasma therapies for infectious diseases
- Products currently in use
- Convalescent plasma – drivers/issues
  - considerations for use
- Initiatives to support potential use

# Background

## Plasma therapies for infectious diseases

- Based on the concept of passive immunization (PI)
- PI is a technique to achieve short term immunisation against infectious disease agents by administrating pathogen specific antibodies
- whole blood, plasma, serum or immune globulin concentrates
- consider the use of convalescent plasma or serum as a potential addition to other measures of preparedness for and response to infectious disease epidemics

# History

## Past use

- In 1890 Emil von Behring first demonstrated antibodies effective as a therapeutic for diphtheria. Nobel prize 1901.
- Supported growth of pharma industry.
- Successfully used to treat many infectious diseases including anthrax, plague, scarlet fever, measles, tularemia, diphtheria, dysentery, meningococcal meningitis, rabies, pneumococcal pneumonia
- Use declined significantly after the advent of antibiotics.


West German postage stamp (1954) commemorating Paul Ehrlich and Emil von Behring

# Current use

- Human and animal derived immunoglobulin concentrates remain important therapies for a variety of viral and bacterial infectious diseases.

- European monographs for human immunoglobulin against:

  viruses Hepatitis A, Hepatitis B, measles, rabies, rubella, varicella and normal (hepatitis A, measles, poliomyelitis or rubella)

- European monographs for animal immunoglobulin against:

  bacterial toxins – botulinum, diphtheria, gangrene, tetanus

# Current use

- In Australia the following human immunoglobulins are supplied under the national supply arrangements (reimbursed): CMV, Hepatitis B, Zoster and normal (to treat susceptible contacts of an indicated infectious disease (hepatitis A, measles, poliomyelitis or rubella)) https://www.blood.gov.au/national-product-list

- Other human immunoglobulins approved for supply in Australia but NOT under national supply arrangements include rabies and tetanus  immunoglobulin

# Future use – convalescent plasma

## Definition

- **plasma obtained from a person who has recovered from an infectious disease and considered to be especially rich in antibodies against the infectious agent of the disease**

https://www.merriam-webster.com/dictionary/convalescent%20serum

# Future use – convalescent plasma

## Some drivers for use

- Rapidly emerging virus epidemic associated with high morbidity or mortality
- Especially early in the event, prior to availability of effective vaccines and antiviral therapies
- Based on the concept of passive immunization
- Supported by historical experience

- Part of epidemic preparedness

# Future use – convalescent plasma

## Evidence base

- Precedent in the modern era for effective management of Argentine Hemorrhagic Fever (Junin Virus) with convalescent immune plasma as part of a nationally organized response[1].
- More recently other agents have also been targeted including Ebola[2,3] .
- Other trials but low level evidence (small numbers, no control arm)

1. Maiztegui J, Fernandez NJ, De Damilano AJ. Efficacy of immune plasma in treatment of Argentine haemorrhagic fever and association between treatment and a late neurological syndrome. Lancet 1979; 314:8154, 1216-1217.
2. Van Griensven J, Edwards T, de Lamballerie X, et al. Evaluation of convalescent plasma for Ebola virus disease in Guinea. .N Engl J Med 2016; 374: 33-42.
3. Van Griensven, J, Edwards, T, Baize, S. Efficacy of Convalescent Plasma in Relation to Dose of Ebola Virus Antibodies. N Engl J Med 2016; 375:2307-2309.
4. Cheng et al. Eur J Clin Microbiol Infect Dis (2005) 24: 44–46

# Future use – convalescent plasma

## Issues

- Potential efficacy dependent generation of neutralizing antibodies or otherwise mediate an effective immune response
- Effective therapeutic dose
- Use of serum, plasma or immunoglobulin concentrate
- Preparation of an immunoglobulin concentrate, higher potency and greater consistency (multiple donors)
- Availability and feasibility of assays useful to select donations likely to be therapeutic, e.g. based on high titer of a total or neutralizing antibody

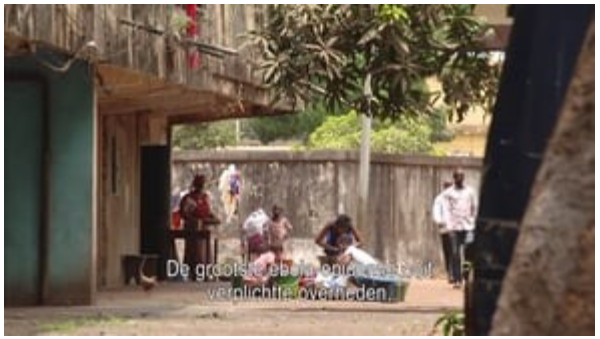
# Future use – convalescent plasma

## Issues

- Potential harm including risk of unintended transmission of undetected infectious agents present in the donor or immune enhancement due to transferred antibodies exacerbating the disease (eg dengue, use anti-viral immune responses to infect host target cells)
- Using pathogen inactivation and reduction technologies
- In country capability (ethical, scientific, and logistic resource issues)
- Close cooperation with mature regulatory authorities experienced in this field and WHO
- Aim for a timely and controlled approach ensuring safety, as well as documentation and scientific evaluation of outcomes

- http://www.ebolatx.eu/film/

# In country capability

# Future use – convalescent plasma

## Considerations ( from draft WHO BRN position paper)

- Clinical use of convalescent plasma or serum should be regarded as investigational. As an experimental therapy should be ethical safeguards (informed consent of donors and patients, institutional approval, special labeling) and a commitment to gather and report outcome data independently of the outcome of the study.

# Future use – convalescent plasma

## Considerations

- Standards for product manufacturing should maximize safety of donors and recipients.

- Collection and manufacture by trained staff operating under standard operating procedures in accordance with international guidelines[1].

- Assays ideally using nucleic acid amplification technology (NAT) to demonstrate resolution of the infection, titer of (neutralizing) antibodies.

- Use donations that are negative for HBV, HCV, HIV, syphilis or other locally transmitted infections.

- Pathogen inactivation of plasma is highly desirable.

1. WHO guidelines on good manufacturing practices for blood establishments. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty- fifth Report. Geneva, World Health Organization, 2011(WHO Technical Report Series; No. 961, Annex 4). http://www.who.int/bloodproducts/publications/GMP_Bloodestablishments.pdf

# Future use – convalescent plasma

## Considerations

- Criteria for patients to be treated. Case definition for confirmation of disease in a candidate patient. Dosing guidelines (units from at least two different donors). Establish priorities for clinical use (early or advance phase disease).

- General considerations for plasma products are applicable. ABO compatibility if plasma used.

- Outcome monitoring should be oriented towards determination of product safety and efficacy and the rapid communication of best practices. Specimen collection from both donors and recipients (pre- and post-treatment) for retrospective determination of the characteristics of an effective product, dosage regimen and patients having most benefit. Rapid aggregation of clinical experience and dissemination of information.

# Future use – convalescent plasma

## Considerations

- Potential use of small scale immunoglobulin concentrates Technology exists to prepare virally inactivated immunoglobulin concentrates from small pools of plasma units[1].

- Feasibility of large scale production including manufacture of purified immunoglobulins Limited by lack of sufficient donations during early phase of epidemic, for recurrent epidemic consideration of identifying donors and stockpiling product. Issues around export import.

1. El-Ekiaby M, Vargas M, Sayed M, Gorgy G, Goubran H, Radosevic M, Burnouf T. Minipool Caprylic Acid Fractionation of Plasma Using Disposable Equipment: A Practical Method to Enhance Immunoglobulin Supply in Developing Countries. http://dx.doi.org/10.1371/journal.pntd.0003501

# Future use – convalescent plasma

## Summary points for use of convalescent plasma

- Consider candidate intervention in the setting of an expanding viral epidemic of public health concern for which vaccines and antiviral drugs are unavailable.
- Development of the infrastructure to permit safe collection and use of convalescent plasma or serum should be part of national epidemic preparedness.
- Feasibility and medical effectiveness for collection and use of convalescent plasma or serum should be explored through clinical trials.
- Convalescent plasma or serum collections should meet the safety and quality criteria consistent with established regulatory standards.
- Concentrates of immunoglobulins may provide products of higher potency and greater consistency than individual units.

# Future use – convalescent plasma

## Initiatives

- European Commission and European Medicines Agency funding
- WHO guidelines
  - **Use of convalescent whole blood or plasma collected from patients recovered from Ebola virus disease** http://www.who.int/csr/resources/publications/ebola/convalescent-treatment/en/
  - **Ethics of using convalescent whole blood and convalescent plasma during the Ebola epidemic**
  - http://www.who.int/csr/resources/publications/ebola/ethics-convalescent-blood/en/

- WHO Blood Regulators Network position papers http://www.who.int/bloodproducts/brn/en/

# Questions