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TABLE OF CONTENTS

HEADER 1
ABSTRACT 1
BACKGROUND 1
OBJECTIVES 2
METHODS 2
ACKNOWLEDGEMENTS 5
REFERENCES 5
APPENDICES 7
CONTRIBUTIONS OF AUTHORS 8
DECLARATIONS OF INTEREST 8
SOURCES OF SUPPORT 8

[Intervention Protocol]

Ribavirin for treating Crimean Congo haemorrhagic fever

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the effects of ribavirin for treating people with Crimean Congo Haemorrhagic Fever (CCHF).

BACKGROUND

Description of the condition

Crimean Congo haemorrhagic fever (CCHF) is a tick-borne viral disease. The virus that causes CCHF is a Nairovirus, a member of the Bunyaviridiae family. The most common vector of the disease are *Hyalomma* ticks, which spread the disease and also act as a disease reservoir. CCHF is found in Africa, Eastern Europe, the Middle East, and Asia, with further occasional cases in other European countries such as Spain and Greece (Hoogstraal 1979; Zapata 2014; García Rada 2016).

The disease starts with a headache, fever, abdominal pain, musculoskeletal pain, and nausea. Over the next few days this is then followed by gastrointestinal symptoms, including vomiting, diarrhoea, and haemorrhagic rash. After three to five days, a minority of patients progress to severe microvascular instability and the haemorrhagic phase of illness, which is usually manifested first by a petechial rash followed by ecchymosis and bleeding. As the disease progresses into the second week, bleeding can worsen and become characteristically more severe, resulting most commonly in haemorrhage under the skin and within the abdomen. Infection in people is usually due to a tick bite or via contact with infected bodily fluids from humans or animals (Ergönül 2006).

Many infections occur without symptoms and some estimates suggest this occurs in most infections (Bodur 2012). CCHF severity in people who are clinically unwell varies. Different scores to assess severity are used but it remains unclear what proportion of all infections are severe (Swanepoel 1987; Dokuzoguz 2013).

Those at highest risk of contracting the virus are people who work outdoors in CCHF-endemic areas, those who work with large domestic animals, and healthcare workers (Whitehouse 2004). CCHF has been linked to reservoirs such as sheep, goats, hedgehogs, and hares (Causey 1970; Saluzzo 1985; Yen 1985; Shepherd 1987). Human-to-human transmission occurs within families and in healthcare settings, including nosocomial outbreaks. The greatest risk of nosocomial exposure is from splash exposures and needle stick injuries (Conger 2015; Leblebicioglu 2016). Case series studies also suggest that in rare cases airborne transmission from ventilated patients may also occur (Pshenichnaya 2015). Case re-

ports suggest possible sexual transmission, although there is no published evidence of the virus being present in seminal or vaginal fluid (Pshenichnaya 2016). The virus is also transmitted from person-to-person by infected bodily fluids, and is highly infectious. Death rates in people infected can reach up to 50% (Hoogstraal 1979). In endemic areas where high-quality supportive care and access to diagnostics are offered, death rates can be as low as 5% (Leblecioglu 2016).

The disease may become more important in future years because of changes to the habitat of the *Hyalomma* tick vector, which is due in part to changes in the rural landscape from large diffuse habitats to smaller habitats. This is shown to lead to densely populated habitats for the tick vector, which is associated with increasing incidence of the disease (Estrada-Peña 2007). Given the high mortality of patients, the lack of a widely available viable vaccine (Dowall 2016), and an emerging pattern of spread with multiple countries reporting re-emergence of epidemics or new cases (Messina 2015), CCHF should be considered a potential threat to public health.

Description of the intervention

Supportive medical care underpins CCHF treatment, and use of fluids, good nursing care, and blood products in response to changes in the blood's ability to clot are a key components of this (Leblebicioglu 2012). Previous attempts at therapeutic regimens have explored intravenous (IV) immunoglobulin isolated from horses (Hoogstraal 1979), and from recovered patients (Vassilenko 1990), but these are not currently widely used.

Ribavirin is a synthetic nucleoside that is active against a broad spectrum of DNA and RNA viruses (Sidwell 1972). It is one of few drugs shown to be active against CCHF in vitro (Watts 1989). Observational studies show that it could be effective in treating cases of CCHF (Fisher-Hoch 1995; Mardani 2003; Dokuzoguz 2013), although this has been debated (Kalin 2014; Leblebicioglu 2016). Ribavirin is used with interferon to treat people who have Hepatitis C, and is used alone in treating people who have Lassa fever (Debing 2013). Ribavirin is also used in healthcare settings as a form of post-exposure prophylaxis (Leblebicioglu 2016).

Ribavirin has adverse effects, and, alongside the questions about its efficacy, clinicians debate whether to use the drug or not (Ceylan 2013; Oflaz 2015). Some of the adverse effects include risks of haemolysis, arrhythmia, bone marrow suppression, and deranged liver function (EMA 2015). Two previous systematic reviews have shown no clear benefit of ribavirin in people with CCHF, although the available evidence is limited mainly to confounded observational data (Soares-Weiser 2010; Ascioglu 2011).

No alternative therapy has been proposed as the mainstay of therapeutic treatment. Although newer drugs, such as favipiravir, have shown promise in vitro (Oestereich 2014), widespread adoption of new therapies is years away. Current treatment guidelines vary from region to region and country to country, and guidance on who and when to treat with ribavirin varies (DoH South Africa 2014; Kalin 2014).

How the intervention might work

Ribavirin can be given in hospital settings either intravenously or orally, according to World Health Organization (WHO) recommendations (WHO 2015). National guidelines from countries such as South Africa (DoH South Africa 2014), India (NCDC 2011), and Pakistan (NIH 2013), recommend prompt treatment with ribavirin following diagnosis of CCHF. However, these recommendations for management are not based on a robust evidence base (Soares-Weiser 2010). CCHF can be mild or more severe as a disease, and often it is not deemed necessary to treat mild cases of the disease (Ergönül 2004). Questions remain about the overall benefits of ribavirin, how long after the onset of symptoms is it most effective, and whether it is more or less effective in severe cases (Ergönül 2006; Dokuzoguz 2013; Leblecioglu 2016).

Existing studies have mostly been observational in design; therefore conclusions previously drawn from these studies are limited. However, administration of ribavirin early in the disease, when it appears to be at its most effective, has been found to be a promising approach (Dokuzoguz 2013; Ozbey 2014). This fits with the known course of the disease, where the virus is most commonly only present in the blood within the first week following onset of CCHF symptoms (Bente 2013).

Why it is important to do this review

In recent years, CCHF incidence has been increasing in several areas worldwide (Zapata 2014). The controversy surrounding ribavirin use and the benefits of a widely available treatment for CCHF mean an up-to-date review of the existing evidence is required. There are mixed views on whether to treat CCHF with ribavirin given the questions over the balance between potential but unproven benefit and known risks of the drug (Kalin 2014). Therefore it is important to use the data available to address whether ribavirin reduces the number of deaths from a disease where many die, whilst assessing the possibility of harm from serious, life-threatening adverse effects.

OBJECTIVES

To assess the effects of ribavirin for treating people with Crimean Congo Haemorrhagic Fever (CCHF).

METHODS

Criteria for considering studies for this review

Types of studies

- Randomized controlled trials (RCTs), quasi-RCTs, and non-randomized controlled studies of ribavirin compared to any other treatment.
- Cohort studies with ribavirin compared to any other treatment schedule (prospective and retrospective).
- Case-control studies with ribavirin compared to any other treatment schedule.

If data are insufficient by consensus within the review author team, we will also summarize the following cohort studies without comparators (prospective or retrospective), cross-sectional studies, and case series (more than 10 cases).

Types of participants

Children or adults of any age with a confirmed case of CCHF with a laboratory test (immunoglobulin or polymerase chain reaction (PCR)).

Types of interventions

Intervention

Ribavirin (intravenous (IV) or oral).

Control

Supportive care only.

Types of outcome measures

Primary outcomes

- Death (in hospital or 28 days post-admission).

Secondary outcomes

- Death (in hospital or 28 days post-admission) amongst those receiving ribavirin within five days of onset of symptoms and death in those receiving ribavirin after five days.
- Length of hospital stay (days).
- Requirement for transfusion (any blood products, including platelets, fresh frozen plasma, packed red cells, or whole blood).
- Withdrawal of treatment due to serious adverse events.
- Serious adverse events as defined according to the accepted US Food and Drug Administration (FDA) definition of: "if in the view of the investigator or sponsor, the event results in any of the following outcomes: death, life threatening adverse event, inpatient hospitalizations, prolongation of existing hospitalization, disability or permanent damage, congenital abnormality, required intervention to prevent permanent impairment or other serious medical events" (FDA 2016).

Search methods for identification of studies

We will attempt to identify all relevant trials regardless of language or publication status (published, unpublished, in press, and in progress).

Electronic searches

We will search the following databases using the search terms and strategy described in Appendix 1: the Cochrane Infectious Diseases Group Specialized Register; the Central Register of Controlled Trials (CENTRAL), published in the Cochrane Library; MEDLINE (PubMed); Embase (OVID); Science Citation Index-Expanded, Social Sciences Citation index, conference proceedings (Web of Science); and CINAHL (EBSCOHost). We will search regional databases as indicated by the World Health Organization (WHO). We will also search the WHO International Clinical Trials Registry Platform (ICTRP; www.who.int/ictrp/en/) and ClinicalTrials.gov (https://clinicaltrials.gov/ct2/home) for trials in progress, using "ribavirin" and "Crimean Congo haemorrhagic fever" or CCHF as search terms.

Searching other resources

We will search the reference lists of any relevant systematic reviews. We will contact researchers in the field, request information about grey literature and ongoing studies from the WHO, and check reference lists of included studies.

Data collection and analysis

Selection of studies

Two review authors will independently screen all citations and abstracts identified in the search according to predefined inclusion criteria, as outlined above. We will obtain the full-text reports of all potentially eligible studies or studies we are unclear about. Two review authors will independently screen these full-text articles. We will resolve any disagreements through discussion and if necessary we will consult a third review author. We will list all studies excluded after full-text assessment and their reasons for exclusion in a 'Characteristics of excluded studies' table. We will illustrate the study selection process in a PRISMA diagram.

Data extraction and management

One review author will extract data using pre tested data extraction forms. A second review author will crosscheck the extracted data. We will resolve any disagreements about data extraction by referring to the study report and through discussion. We will attempt to contact the study authors where data are insufficient or missing.

We will extract data using a tool individualized for the inclusion criteria described above, including dose and method of administration (oral or IV) adult or paediatric populations, location, setting, design, study size, dates, and various clinical parameters.

Assessment of risk of bias in included studies

Two review authors will assess the risk of bias of each included study; we will resolve any disagreements through discussion and we will consult a third review author if necessary. For RCTs or quasi-RCTs, we will use the Cochrane Risk of Bias tool for RCTs (Higgins 2011a). For observational studies, we will use the Cochrane Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I); (Sterne 2016).

We will use ROBINS-I to assess the risk of bias for all included observational studies. We will assess risk of bias through a hierarchy of domains, starting with critical then serious, moderate, and low. If any domain reaches critical risk of bias we will not continue with the assessment, as further evaluation will not influence how we assess the certainty of the evidence.

We will perform an analysis that only includes RCTs and observational studies at serious, moderate, or low risk of bias.

We will perform an analysis of data including studies with a critical risk of bias if this helps understanding of obvious confounding and provides an assessment of the degree to which confounding may influence effect estimates.

Measures of treatment effect

For dichotomous outcomes, we will use risk ratios (RR) with their 95% confidence intervals (CIs). For continuous data we will use mean differences with their 95% CIs.

Unit of analysis issues

For cluster-RCTs, or cluster non-randomized trials, we will extract adjusted measures of effect where possible. If the included study does not perform any adjustment for clustering, we will adjust the raw data ourselves using an intra cluster correlation coefficient (ICC). If the study authors do not report an ICC value in the published article, we will either obtain this value from similar studies or we will estimate the ICC value. We will not present results from cluster-randomized trials that are not adjusted for clustering. If we estimate the ICC value, we will perform sensitivity analyses to investigate the robustness of our analyses.

If we identify studies for inclusion that have multiple intervention arms, we will include data from these studies by either combining treatment arms, or by splitting the control group so that we only include participants once in the meta-analysis.

Dealing with missing data

We will attempt to contact the study authors to obtain missing data when the lack of reporting of necessary data restricts the use of the study. We anticipate that we may not be able to reach the study author(s) of older publications. We will use an available-case analysis, unless incomplete outcome data is such that we consider the study to be at high risk of bias; in which case we may use imputation to investigate the impact of this missing data.

Assessment of heterogeneity

We will examine the included studies to determine whether there is heterogeneity in terms of co-intervention, level of supportive care available, and risk of bias in the included studies.

We will inspect forest plots visually to assess whether statistical heterogeneity is present. We will deem CIs that do not overlap as an indication of statistical heterogeneity. We will also perform the Chi^2 test using a cut-off point of $P < 0.10$ to indicate statistical heterogeneity, and we will use the I^2 statistic to quantify heterogeneity. We will interpret the I^2 statistic value according to guidance from the *Cochrane Handbook of Systematic Reviews of Interventions* (Higgins 2011a).

Assessment of reporting biases

If applicable, we will use funnel plot analysis or statistical tests (such as the Egger regression test), or both, to assess for publication bias. We will only perform funnel plot analysis if there are more than 10 studies in any meta-analysis.

Data synthesis

We will consider performing a meta-analysis using Review Manager 5 (RevMan 5) if it is appropriate to do so (RevMan 2014). If it is inappropriate to perform a meta analysis, we will present the results in tables.

For observational studies, whenever possible, we will combine the adjusted point estimates and standard errors in the logarithm scale using the generic inverse-variance random-effects methods. We will perform meta-analysis if appropriate; although in observational studies with a high risk of bias, this will be to illustrate the potential size of the effect of confounding.

We will use the GRADE approach to assess the certainty of the evidence and we will create 'Summary of findings' tables and Evidence Profiles (GRADEpro 2015). Data from observational studies will start as low quality, but we may upgrade this to moderate or high quality if the pooled estimates reveal a large magnitude of

effect, negligible concerns about confounders, or a strong dose-response gradient.

If there are differences within populations we combine in meta-analyses that impact upon treatment effect, such as dosing, supportive care, or age, we will use the random-effects model to reflect this.

Subgroup analysis and investigation of heterogeneity

If unexplained heterogeneity occurs we will perform subgroup analyses of the results to assess whether the effect of ribavirin is influenced by any of the following factors.

- Severity of symptoms: severe, moderate, mild.
- Early and late treatment: number of days from onset of symptoms.
- Duration of treatment, presence of severe gastrointestinal symptoms and route of administration.
- Age (children versus adults). Children are defined as under 16 years of age.

Sensitivity analysis

If we estimate an ICC to adjust the results from cluster trials, we will perform sensitivity analyses to investigate the robustness of our analyses. If necessary we will perform a sensitivity analysis and consider exclude studies that are at high risk of bias according to the Cochrane Risk of Bias tool for RCTs (Higgins 2011b), and serious risk of bias according to ROBINS-I tool for observational studies (Sterne 2016).

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. MEDLINE (PubMed) search strategy

1) "Hemorrhagic Fever, Crimean"[Mesh]) OR "Hemorrhagic Fever Virus, Crimean-Congo"[Mesh])
2) CCHF OR "Crimean Congo hemorrhagic fever" or "Crimean Congo haemorrhagic fever" Field: Title/Abstract
3) 1 or 2
4) "ribavirin"[MeSH Terms] OR "ribavirin"[All Fields]
5) 3 and 4
This is the preliminary search strategy for MEDLINE (Pubmed) and will be adapted for other electronic databases. We will report all search strategies in full in the final version of the review.

CONTRIBUTIONS OF AUTHORS

SJ and RM drafted the protocol, NM, IM, AK, and BSB aided in development of the protocol. All authors read and approved the final protocol draft.

DECLARATIONS OF INTEREST

SJ has no known conflicts of interest.

RM has no known conflicts of interest.

NM has no known conflicts of interest.

IM has no known conflicts of interest.

AK has no known conflicts of interest.

BSB has no known conflicts of interest.

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