# Clinical management strategies of Novel Coronavirus (HCoV EMC)

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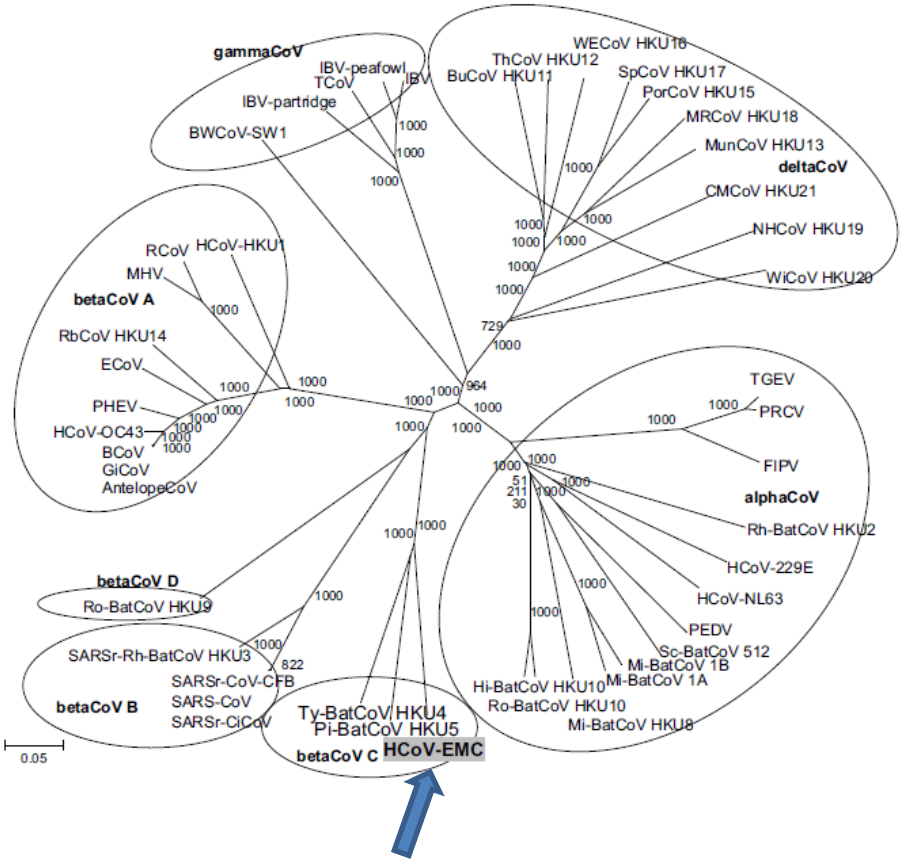
# Background

23/9/2012 :
The WHO reported 2 laboratory-confirmed cases of
severe respiratory disease associated with a novel coronavirus - HCoV-EMC
(Erasmus Medical Center in Rotterdam, the Netherlands)

Order : *Nidovirales*
Family : *Coronaviridae*
Genus : betacoronavirus - Group C

Enveloped positive-sense
single stranded
RNA virus
genome size of about 30 kb

Closely related to the
bat coronaviruses HKU4 and HKU5




Journal of Infection (2012) **65**, 477–489

# Human Betacoronavirus 2c EMC/2012–related Viruses in Bats, Ghana and Europe

**Augustina Annan,[1] Heather J. Baldwin,[1] Victor Max Corman,[1] Stefan M. Klose, Michael Owusu, Evans Ewald Nkrumah, Ebenezer Kofi Badu, Priscilla Anti, Olivia Agbenyega, Benjamin Meyer, Samuel Oppong, Yaw Adu Sarkodie, Elisabeth K.V. Kalko,[2] Peter H.C. Lina, Elena V. Godlevska, Chantal Reusken, Antje Seebens, Florian Gloza-Rausch, Peter Vallo, Marco Tschapka, Christian Drosten, and Jan Felix Drexler**

We screened fecal specimens of 4,758 bats from Ghana and 272 bats from 4 European countries for betacoronaviruses. Viruses related to the novel human betacoronavirus EMC/2012 were detected in 46 (24.9%) of 185 *Nycteris* bats and 40 (14.7%) of 272 *Pipistrellus* bats. Their genetic relatedness indicated EMC/2012 originated from bats.

Coronaviruses (CoVs) are enveloped viruses with a positive-sense, single-stranded RNA genome (*1*). CoVs are classified into 4 genera: *Alphacoronavirus*, *Betacoronavirus* (grouped further into clades 2a–2d), *Gammacoronavirus*, and *Deltacoronavirus*. Two human coronaviruses (hCoVs), termed hCoV-OC43 and –229E, have been known since the 1960s and cause chiefly mild respiratory disease (*2*). In 2002–2003, an outbreak of severe acute respiratory syndrome (SARS) leading to ≈850 deaths was caused by a novel group 2b betacoronavirus, SARS-CoV (*3*). A likely animal reservoir for SARS-CoV was identified in rhinolophid bats (*4*,*5*). In the aftermath of the SARS pandemic, 2 hCoVs, termed hCoV-NL63 and -HKU1, and numerous novel bat CoVs were described.

In September 2012, health authorities worldwide were notified of 2 cases of severe respiratory disease caused by a novel hCoV (*6*,*7*). This virus, termed EMC/2012, was related to the 2c betacoronavirus clade, which had only been known to contain *Tylonycteris bat coronavirus* HKU4 and *Pipistrellus bat coronavirus* HKU5 (*8*).

We previously identified highly diversified alphacoronaviruses and betacoronaviruses, but not clade 2c betacoronaviruses, in bats from Ghana (*9*). We also identified sequence fragments from a 2c betacoronavirus from 1 *Pipistrellus* bat in Europe (*10*). In this study, we analyzed an extended sample of 4,758 bats from Ghana and 272 bats from 4 European countries.

## The Study

Fecal specimens were collected from 10 bat species in Ghana and 4 *Pipistrellus* species in Europe (Table 1). Bats were caught during 2009–2011 with mist nets, as described (*9*), in 7 locations across Ghana and 5 areas in Germany, the Netherlands, Romania, and Ukraine (Figure 1). The species, age, sex, reproductive status, and morphologic measurements of the bats were recorded. Fecal pellets were

Annan A, Baldwin HJ, Corman VM, Klose SM, Owusu M, Nkrumah EE, et al. Human betacoronavirus 2c EMC/2012–related viruses in bats, Ghana and Europe. Emerg Infect Dis [Internet]. 2013 Mar. http://dx.doi.org/10.3201/eid1903.121503

# Epidemiology update on Novel Coronavirus

- Laboratory confirmed cases to date: 14 (8 deaths) - > 50% mortality
  - Saudi Arabia: 7 (5 deaths)
  - Jordan: 2 (2 deaths)
  - UK: 4 (1 patient from Qatar – receiving treatment; 1 patients travelled from Pakistan/Saudi Aradia – receiving treatment ; 2 from UK- 1 recovered, 1 death)
  - Germany: 1 (patient from Qatar – discharged)

# Details of 14 confirmed cases (as of 6/3/13)

| Case No. | Date of Onset | Age (years) | Sex | Probable place of infection | Date reported | Outcome | Clusters | Remark | |
|---|---|---|---|---|---|---|---|---|---|
| 1 | April 2012 | 45 | F | Jordan | 30/11/2012 | Dead | Zarqa hospital (nurse) | Retrospective testing a cluster of 11 pneumonia cases (7 nurses and 1 doctor) which occurred in an intensive care unit. | |
| 2 | April 2012 | 25 | M | Jordan | 30/11/2012 | Dead | Zarqa hospital (intern) | | |
| 3 | 13/06/2012 | 60 | M | Kingdom of Saudi Arabia | 20/09/2012 | Dead | No | Isolate was obtained from lung tissue. | |
| 4 | 03/09/2012 | 49 | M | Qatar/ Kingdom of Saudi Arabia | 23/09/2012 | Alive/ Hospitalized | No | Travel history to Saudi Arabia. Transferred to UK hospital. | ECMO |
| 5 | 10/10/2012 | 45 | M | Kingdom of Saudi Arabia | 04/11/2012 | Alive | No | | |
| 6 | 12/10/2012 | 45 | M | Qatar | 23/11/2012 | Alive | No | Transferred to Germany hospital (discharged). | |
| 7 | 03/11/2012 | 31 | M | Kingdom of Saudi Arabia | 20/11/2012 | Alive | Family A in Riyadh | 1 more family member, who had a similar illness and recovered but tested negative by PCR, was not included. | |
| 8 | 28/10/2012 | 39 | M | Kingdom of Saudi Arabia | 23/11/2012 | Dead | Family A in Riyadh | | |
| 9 | October 2012 | 70 | M | Kingdom of Saudi Arabia | 28/11/2012 | Dead | Family A in Riyadh (father) | | |
| 10 | 24/01/2013 | 60 | M | Pakistan/ Kingdom of Saudi Arabia | 11/02/2013 | Alive/ Hospitalized | Family B in UK | UK citizen. Travel history to Pakistan and Saudi Arabia. Co-infected with Influenza A(H1N1) pdm 2009 | ECMO |
| 11 | 06/02/2013 | Adult | M | United Kingdom | 12/02/2013 | Dead | Family B in UK (son of case 10) | | ECMO |
| 12 | 05/02/2013 | Adult | F | United Kingdom | 15/02/2013 | Alive/ Recovered (mild disease) | Family B in UK | Limited exposure to case 10 on 3 occasions while he was in hospital | |
| 13 | Unknown | Unknown | Unknown | Kingdom of Saudi Arabia | 21/02/2013 | Dead | No | Hospitalized on 29 Jan and died on 10 Feb 2013 | |
| 14 | Unknown | 69 | M | Kingdom of Saudi Arabia | 6/03/2013 | Dead | No | Hospitalized on 10 Feb and died on 19 Feb 2013 | |

- Rapid Risk Assessment: Severe respiratory disease associated with a novel coronavirus Technical reports - 19 Feb 2013
- http://www.who.int/csr/don/2013_02_21/en/index.html
- http://www.who.int/csr/don/2013_03_06/en/index.html

(體外膜氧合)

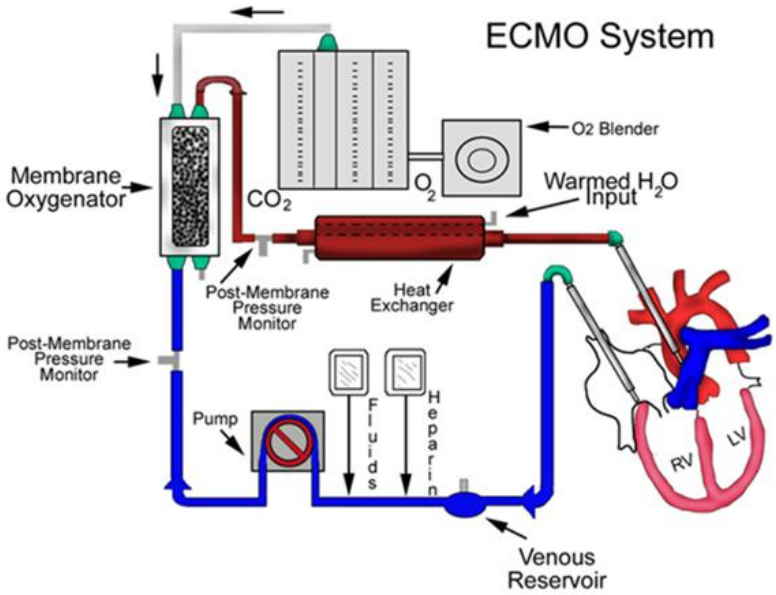
# Extracorporeal Membrane Oxygenation for 2009 Influenza A(H1N1) Acute Respiratory Distress Syndrome

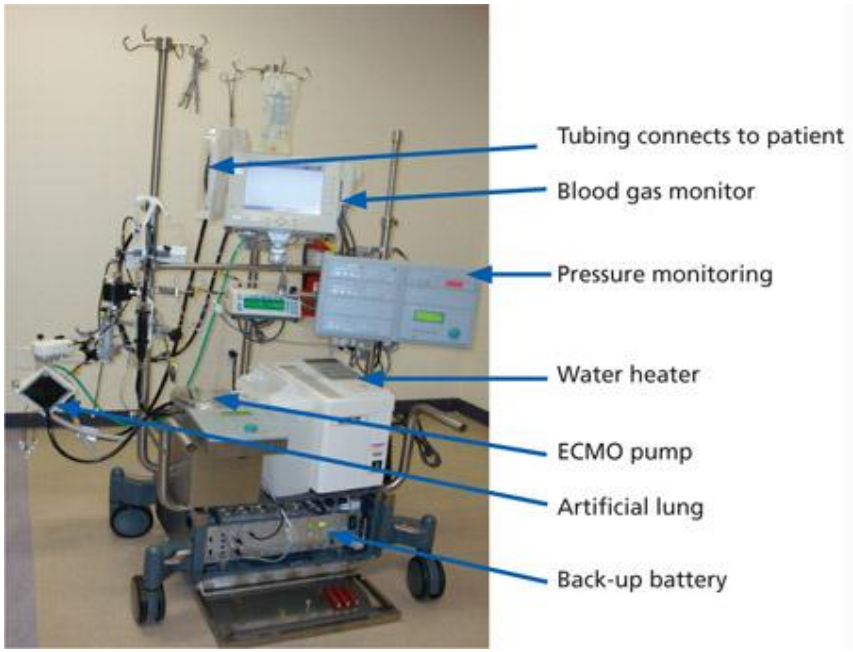
The Australia and New Zealand Extracorporeal Membrane Oxygenation (ANZ ECMO) Influenza Investigators*

JAMA. 2009;302(17):1888-1895

## Hong Kong's experience on the use of extracorporeal membrane oxygenation for the treatment of influenza A (H1N1)

Hong Kong Med J 2010;16:447-54



# INTERIM GUIDANCE DOCUMENT

## Clinical management of severe acute respiratory infections when novel coronavirus is suspected: What to do and what not to do



**Mainly supportive treatment**

http://www.who.int/csr/disease/coronavirus_infections/InterimGuidance_ClinicalManagement_NovelCoronavirus_11Feb13.pdf

# Introduction

The emergence of novel coronavirus in 2012 (see http://www.who.int/csr/disease/coronavirus_infections/en/index.html for the latest updates) has presented challenges for clinical management.

Pneumonia has been the most common clinical presentation; five patients developed Acute Respiratory Distress Syndrome (ARDS). Renal failure, pericarditis and disseminated intravascular coagulation (DIC) have also occurred.

Our knowledge of the clinical features of coronavirus infection is limited and no virus-specific prevention or treatment (e.g. vaccine or antiviral drugs) is available. Thus, this interim guidance document aims to help clinicians with supportive management of patients who have acute respiratory failure and septic shock as a consequence of severe infection. Because other complications have been seen (renal failure, pericarditis, DIC, as above) clinicians should monitor for the development of these and other complications of severe infection and treat them according to local management guidelines.

As all confirmed cases reported to date have occurred in adults, this document focuses on the care of adolescents and adults. Paediatric considerations will be added later.

http://www.who.int/csr/disease/coronavirus_infections/InterimGuidance_ClinicalManagement_NovelCoronavirus_11Feb13.pdf

SECTION 1

# Early recognition and management

## Give empiric antimicrobials to treat suspected pathogens, including community-acquired pathogens

Although the patient may be suspected to have novel coronavirus infection, administer appropriate empiric antimicrobials as soon as possible for community-acquired pathogens based on local epidemiology and guidance until the diagnosis is confirmed. Empiric therapy can then be adjusted on the basis of laboratory testing results.

## Use conservative fluid management in patients with SARI when there is no evidence of shock

Patients with SARI should be treated cautiously with intravenous fluids, because aggressive fluid resuscitation may worsen oxygenation, especially in settings where there is limited availability of mechanical ventilation (*7*).

## Do not give high-dose systemic corticosteroids or other adjunctive therapies for viral pneumonitis outside the context of clinical trials

Prolonged use of systemic high-dose corticosteroids can result in serious adverse events in patients with SARI, including opportunistic infection, avascular necrosis, new health-care-associated bacterial infection and possibly prolonged viral replication. Therefore, corticosteroids should be avoided unless they are indicated for another reason (*8*).

http://www.who.int/csr/disease/coronavirus_infections/InterimGuidance_ClinicalManagement_NovelCoronavirus_11Feb13.pdf

# SARS: Systematic Review of Treatment Effects

**Lauren J. Stockman[1,2*], Richard Bellamy[3], Paul Garner[4]**

1 Centers for Disease Control and Prevention, Respiratory and Enteric Viruses Branch, Atlanta, Georgia, United States of America, 2 Department of Veterans' Affairs, Atlanta Research and Education Foundation, Decatur, Georgia, United States of America, 3 James Cook University Hospital, Middlesbrough, United Kingdom, 4 Liverpool School of Tropical Medicine, Liverpool, United Kingdom

**Table 1.** Summary of the Evidence for Benefit or Harm of Drugs Used to Treat SARS

| Treatment | Inconclusive[a] | Possible Harm[a] | Total Studies with Evidence (English and Chinese)[b] |
|---|---|---|---|
| Ribavirin | 26 | 4 | 30 |
| Corticosteroid | 25 | 4 | 29 |
| LPV/r | 2 | 0 | 2 |
| IFN-α | 3 | 0 | 3 |
| Convalescent plasma or Immunoglobulin | 7 | 0 | 7 |

[a]Studies were classified into six categories, but there were four categories without any studies: "possible benefit," "possible harm," "definite benefit," "definite harm" (see Box 1).
[b]Studies totalled 54; some reported on more than one drug.
DOI: 10.1371/journal.pmed.0030343.t001

# SARS experience – lopinavir/ritonavir (kaletra)

## Treatment of severe acute respiratory syndrome with lopinavir/ritonavir: a multicentre retrospective matched cohort study

## 以快利佳/諾億亞治療嚴重急性呼吸系統綜合症：多個中心的回顧性對照組別研究

- **lopinavir 400 mg/ritonavir 100 mg** orally **every 12 hours** to the standard regimen

- given for **10 to 14 days**, depending on disease severity and patient tolerance


**Objectives.** To investigate the possible benefits and adverse effects of the addition of lopinavir/ritonavir to a standard treatment protocol for the treatment of severe acute respiratory syndrome.

**Design.** Retrospective matched cohort study.

**Setting.** Four acute regional hospitals in Hong Kong.

**Patients and methods.** Seventy-five patients with severe acute respiratory syndrome treated with lopinavir/ritonavir in addition to a standard treatment protocol adopted by the Hospital Authority were matched with controls retrieved from the Hospital Authority severe acute respiratory syndrome central database. Matching was done with respect to age, sex, the presence of co-morbidities, lactate dehydrogenase level and the use of pulse steroid therapy. The 75 patients treated with lopinavir/ritonavir were divided into two subgroups for analysis: lopinavir/ritonavir as initial treatment, and lopinavir/ritonavir as rescue therapy. These groups were compared with matched cohorts of 634 and 343 patients, respectively. Outcomes including overall death rate, oxygen desaturation, intubation rate, and use of pulse methylprednisolone were reviewed.

**Results.** The addition of lopinavir/ritonavir as initial treatment was associated with a reduction in the overall death rate (2.3%) and intubation rate (0%), when compared with a matched cohort who received standard treatment (15.6% and 11.0% respectively, $P<0.05$) and a lower rate of use of methylprednisolone at a lower mean dose. The subgroup who had received lopinavir/ritonavir as rescue therapy, showed no difference in overall death rate and rates of oxygen desaturation and intubation compared with the matched cohort, and received a higher mean dose of methylprednisolone.

**Conclusion.** The addition of lopinavir/ritonavir to a standard treatment protocol as an initial treatment for severe acute respiratory syndrome appeared to be associated with improved clinical outcome. A randomised double-blind placebo-controlled trial is recommended during future epidemics to further evaluate this treatment.


*Hong Kong Med J 2003;9:399-406*

# SARS experience – lopinavir/ritonavir (kaletra)

## Treatment of severe acute respiratory syndrome with lopinavir/ritonavir: a multicentre retrospective matched cohort study

**Table 3. Comparison of outcomes for the group given LPV/r as initial treatment and a matched cohort***

| | LPV/r as initial treatment, n=44 Crude rate or mean (95% CI) | Matched cohort, n=634 Standardised rate or mean† (95% CI) | P value |
|---|---|---|---|
| Death rate (%) | 2.3 (0-6.8) | 15.6 (9.8-22.8) | <0.05 |
| Intubation rate (%) | 0 | 11.0 (7.7-15.3) | <0.05 |
| Desaturation rate (SaO2≤95%) [%] | 68.2 (52.3-81.8) | 84.5 (74.4-95.2) | NS‡ |
| Proportion requiring pulse methylprednisolone rescue (%) | 27.3 (11.4-40.9) | 55.4 (47.6-63.9) | <0.05 |
| Mean pulse methylprednisolone dose (g) | 1.6 (1.1-2.0) | 3.0 (2.8-3.2) | <0.05 |

* Matched on age, sex, presence/absence of co-morbidity, and initial lactate dehydrogenase level
† Standardised based on the percentage distribution of subjects of the treated group across the prognostic strata in Table 1
‡ NS not significant

**Table 4. Comparison of outcomes of the group given LPV/r as rescue treatment and a matched cohort***

| | LPV/r as rescue, n=31 Crude rate or mean (95% CI) | Matched cohort, n=343 Standardised rate or mean† (95% CI) | P value |
|---|---|---|---|
| Death rate (%) | 12.9 (0-25.8) | 14.0 (5.2-26.3) | NS‡ |
| Intubation rate (%) | 9.7 (0-22.6) | 18.1 (9.0-29.7) | NS |
| Desaturation rate (SaO2≤95%) [%] | 93.5 (80.6-100) | 92.1 (75.9-100) | NS |
| Mean pulse methylprednisolone dose (g) | 3.8 (3.5-4.2) | 3.0 (2.9-3.2) | <0.05 |

* Matched on age, sex, presence/absence of co-morbidity, lactate dehydrogenase level before pulse methylprednisolone, and use of pulse methylprednisolone
† Standardised based on the percentage distribution of subjects of the treated group across the prognostic strata in Table 1
‡ NS not significant

*Hong Kong Med J 2003;9:399-406*

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**RESPIRATORY INFECTION**

## Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings

C M Chu, V C C Cheng, I F N Hung, M M L Wong, K H Chan, K S Chan, R Y T Kao, L L M Poon, C L P Wong, Y Guan, J S M Peiris, K Y Yuen, on behalf of the HKU/UCH SARS Study Group*

**Background:** The clinical response of patients with severe acute respiratory syndrome (SARS) to a combination of lopinavir/ritonavir and ribavirin was examined after establishing the in vitro antiviral susceptibility of the SARS associated coronavirus to a panel of antiviral agents.

**Methods:** The in vitro susceptibility of the prototype of SARS associated coronavirus to a panel of nucleoside analogues and protease inhibitors currently licensed for clinical use was studied. Forty one patients with SARS followed for 3 weeks were treated with a combination of lopinavir/ritonavir and ribavirin. The clinical progress and virological outcomes were monitored and compared with 111 patients treated with ribavirin only who served as historical controls.

**Results:** In vitro antiviral activity against SARS associated coronavirus was demonstrated for lopinavir and ribavirin at concentrations of 4 μg/ml and 50 μg/ml, respectively, only at 48 hours. The adverse clinical outcome (ARDS or death) was significantly lower in the treatment group than in the historical controls (2.4% *v* 28.8%, $p<0.001$) at day 21 after the onset of symptoms. The adverse outcome remained significantly lower in the treatment group than in the controls—both those diagnosed early ($p<0.001$) and those diagnosed later in the course of the epidemic ($p=0.002$)—but there was no significant difference in adverse outcome rates between the two time periods ($p=0.548$). No time related difference in outcome was observed in the control groups. A reduction in steroid usage and nosocomial infections was seen in patients initially treated with lopinavir/ritonavir, and these patients had a decreasing viral load and rising peripheral lymphocyte count. Multivariate analysis showed that age, hepatitis B carrier status, and lack of treatment with this antiviral combination were independent predictors of an adverse outcome. Lopinavir/ritonavir treatment was associated with a better outcome even when adjusted for baseline lactate dehydrogenase level.

**Conclusions:** The apparent favourable clinical response with lopinavir/ritonavir and ribavirin supports further randomised placebo controlled trials in patients with SARS.

*Thorax* 2004;**59**:252–256. doi: 10.1136/thorax.2003.012658

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**Lopinavir (400 mg)/ritonavir (100 mg)** orally every 12 hours for **14 days**

Both historical controls and lopinavir/ritonavir treated group given ribavirin and corticosteroid according to the same protocol

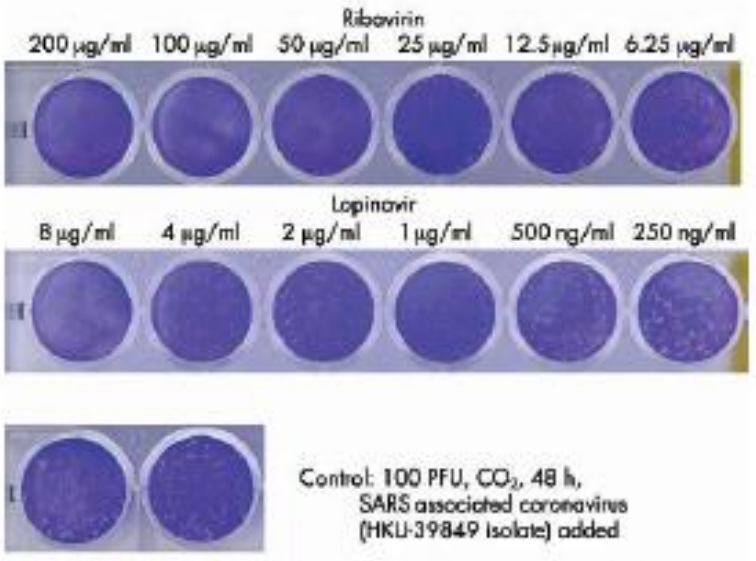


Figure 1 Dose dependent antiviral effects of ribavarin and lopinavir on SARS coronavirus. In vitro antiviral susceptibility testing showed that the cytopathic effect was inhibited by lopinavir at 4 μg/ml and ribavirin at 50 μg/ml after 48 hours of incubation.

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**Table 1** Baseline characteristics and 21 day adverse outcome (death or development of ARDS requiring intensive care) of historical controls and treatment group

| | Historical controls (n = 111) | Treatment group (n = 41) | p value |
|---|---|---|---|
| Mean (SD) age (years) | 42.1 (14.7) | 39.4 (15.2) | 0.32 |
| Male:female ratio | 48:63 | 10:31 | 0.039 |
| Active co-morbid condition | 22 (19.8%) | 6 (14.6%) | 0.464 |
| Chronic hepatitis B infection | 11 (9.9%) | 1 (2.4%) | 0.182 |
| Mean (SD) duration of symptoms to admission (days) | 2.61 (2.3) | 1.85 (1.5) | 0.05 |
| Apparently normal chest radiograph on admission | 23 (20.7%) | 11 (26.8%) | 0.511 |
| Multilobar involvement on initial chest radiograph | 29 (26.1%) | 5 (12.2%) | 0.081 |
| NPA RT-PCR positive at diagnosis | 41 (36.9%) | 14 (34.1%) | 0.850 |
| Mean (SD) haemoglobin (g/dl) | 13.3 (1.6) | 13.5 (1.4) | 0.468 |
| Mean (SD) initial total peripheral WBC count ($\times 10^9$/l) | 6.4 (2.2) | 6.7 (3.0) | 0.420 |
| Mean (SD) initial lymphocyte count ($\times 10^9$/l) | 1.0 (0.5) | 0.9 (0.3) | 0.297 |
| Mean (SD) initial platelet count ($\times 10^9$/l) | 169 (44) | 199 (77) | 0.023 |
| Median (IRQ) initial LDH (IU/l) | 401 (344–467) | 276 (197–336) | <0.001 |
| Median (IRQ) cumulative pulse methylprednisolone dose (g) | 1.5 (1.0–3.0) | 2.0 (0–3.0) | 0.477 |
| Development of ARDS or death within 21 days | 32 (28.8%) | 1 (2.4%) | <0.001 |
| Death/ARDS at day 21 | 7 (6.3%)/25 (22.5%) | 0 (0%)/1 (2.4%) | – |

NPA = nasopharyngeal aspirate; WBC = white blood cell; LDH = lactate dehydrogenase; ARDS = acute respiratory distress syndrome.

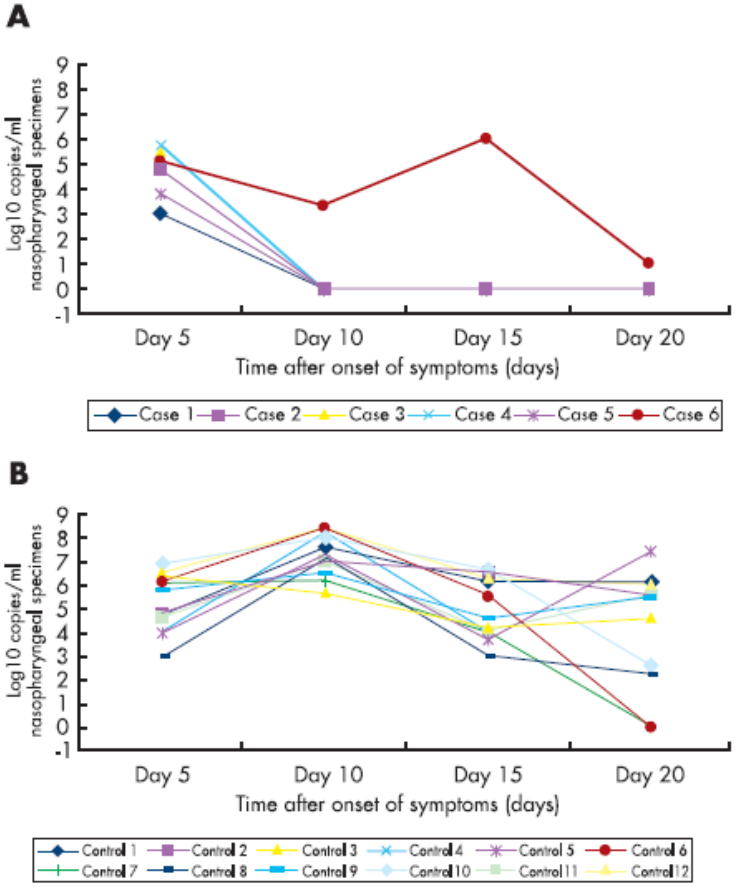


**Figure 2** (A) Change in viral load by sequential quantitative RT-PCR for SARS associated coronavirus in nasopharyngeal swabs of six patients in the initial treatment subgroup. Note that case 6 was given pulse methylprednisolone on day 7. (B) Change in viral load by sequential quantitative RT-PCR for SARS associated coronavirus in nasopharyngeal swabs of 12 patients in the historical control group.

Thorax 2004;59:252–256. doi: 10.1136/thorax.2003.012658

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**Table 2** Independent risk factors predicting adverse outcome of death or development of acute respiratory distress syndrome (ARDS) requiring intensive care within 21 days

| Variables | Adjusted odds ratio (95% CI) | p value |
|---|---|---|
| Age group (years) | | 0.013 |
| 21–40 | 1.00 | – |
| 41–60 | 1.49 (0.56 to 3.98) | 0.431 |
| 61+ | 4.69 (1.57 to 13.97) | 0.006 |
| HBsAg positive patients | 6.35 (1.67 to 24.08) | 0.007 |
| Treatment | | |
| Controls | 1.00 | – |
| Treatment group | 0.07 (0.01 to 0.55) | 0.011 |

HBsAg = Hepatitis B surface antigen.

**Table 3** Adjustment of odds ratio of lopinavir/ritonavir treatment for lactate dehydrogenase (LDH) level with respect to the adverse outcome of death or development of acute respiratory distress syndrome (ARDS) requiring intensive care within 21 days

| Variables | Adjusted odds ratio (95% CI) | p value |
|---|---|---|
| Treatment | | |
| Controls | 1.000 | – |
| Treatment group | 0.076 (0.01 to 0.589) | 0.014 |
| LDH level (per 100 IU/l increase) | 1.155 (0.953 to 1.401) | 0.142 |

*Thorax* 2004;59:252–256. doi: 10.1136/thorax.2003.012658

# SARS: Systematic Review of Treatment Effects

**Lauren J. Stockman[1,2*], Richard Bellamy[3], Paul Garner[4]**

**1** Centers for Disease Control and Prevention, Respiratory and Enteric Viruses Branch, Atlanta, Georgia, United States of America, **2** Department of Veterans' Affairs, Atlanta Research and Education Foundation, Decatur, Georgia, United States of America, **3** James Cook University Hospital, Middlesbrough, United Kingdom, **4** Liverpool School of Tropical Medicine, Liverpool, United Kingdom

| | | | | | |
|---|---|---|---|---|---|
| **Immunoglobulin or Convalescent Plasma** | N/A | There was an improvement in radiographic score 5, 6, and 7 days after treatment with IVIg, compared to day 1. Patients recovered after treatment. | IVIg was given after deterioration on corticosteroid and ribavirin treatment. Cannot tell if improvement was attributed to IVIg. | Inconclusive | (35) |
| | N/A | Death rate: 6.3% early group v 21.9% later group. No adverse reactions seen. Better outcome if convalescent plasma given before day 14 of illness and among those who were still sero-negative for SARS-CoV. | Patients received plasma at different time during illness. Without a control group, cannot be sure that improvement is due to convalescent plasma. | Inconclusive | (36) |
| | N/A | Death: 0/19 vs 5/21 in control. Convalescent plasma associated with a more favourable outcome in SARS patients who deteriorated despite ribavirin and high dose MP. | Either plasma or steroids given at discretion of physician and based on availability of plasma. Steroid group had more co-morbidities. Cannot attribute improvement to treatment alone. | Inconclusive | (37) |
| | Intravenous immunoglobulin | ARDS was associated with significant mortality in SARS patients despite aggressive therapy with ribavirin, steroids and IVIG. | Study looked for associations with ARDS. Not possible to determine specific treatment effect since many different treatments were given together. Treatment determined by physicians and not defined by specific criteria. | Inconclusive | (20) |
| | Intravenous immunoglobulin 1g/kg/day for 2 days | Death rate 19.7%. Authors suggest that IVIG appeared effective in controlling leukopenia and thrombocytopenia. | Lack of control group, underlying conditions in several patients and combination of treatment prevents conclusion on treatment effectiveness. | Inconclusive | (24) |

Inconclusive : could not be discerned from the effects of patient comorbidities, stage of illness, or effect of other treatments

Chinese Literature

| | | | | | |
|---|---|---|---|---|---|
| **Immunoglobulin** | Not specified | Death: 1/96. Corticosteroids, human gamma globulin, interferon-a, and antiviral drugs may be some benefit in shortening clinical course. | Clinical illness in patients (mostly hospital staff) is described but the effect of treatment cannot be evaluated. | Inconclusive | (4) |
| | Not specified | Death 0/15. SARS is mild in children. | All children given ribavirin, steroids and IgG. No information on treatment effect. | Inconclusive | (2) |

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| | | | | | |
|---|---|---|---|---|---|
| **Interferon-alpha** | 9ug/d for 2 days then increased to 15 ug/d if no clinical response | Death: 0/9 in interferon-a +steroid group. Death: 1/13 in steroid only group. IFN-a was well tolerated. Evidence that IFN-a may have more rapid resolution of lung x-ray and better oxygen saturation levels than corticosteroids alone. | Control group was patients admitted at the same time and treated with corticosteroids only or those who declined interferon treatment. Lack of randomization and small sample size makes effect of treatment difficult to conclude. | Inconclusive | (34) |
| | IM 3,000,000 U/day | The combined use of interferon and large dose of immunoglobulin had no obvious effect. | Patients in each group were given CPAP inconsistently. Lack of clear-cut use of any treatment in any group makes it difficult to find an effect. | Inconclusive | (3) |

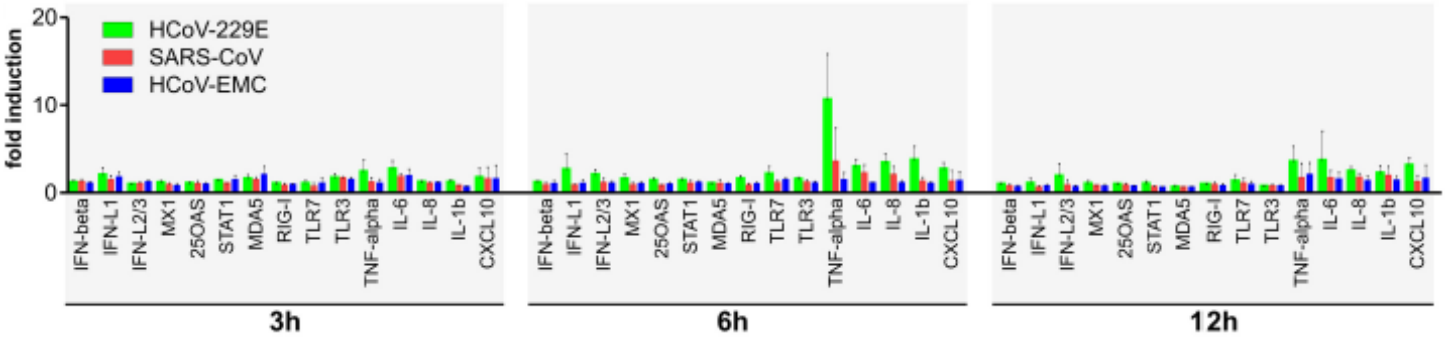
Inconclusive : lack of consistent treatment regimen or suitable control group

Chinese Literature

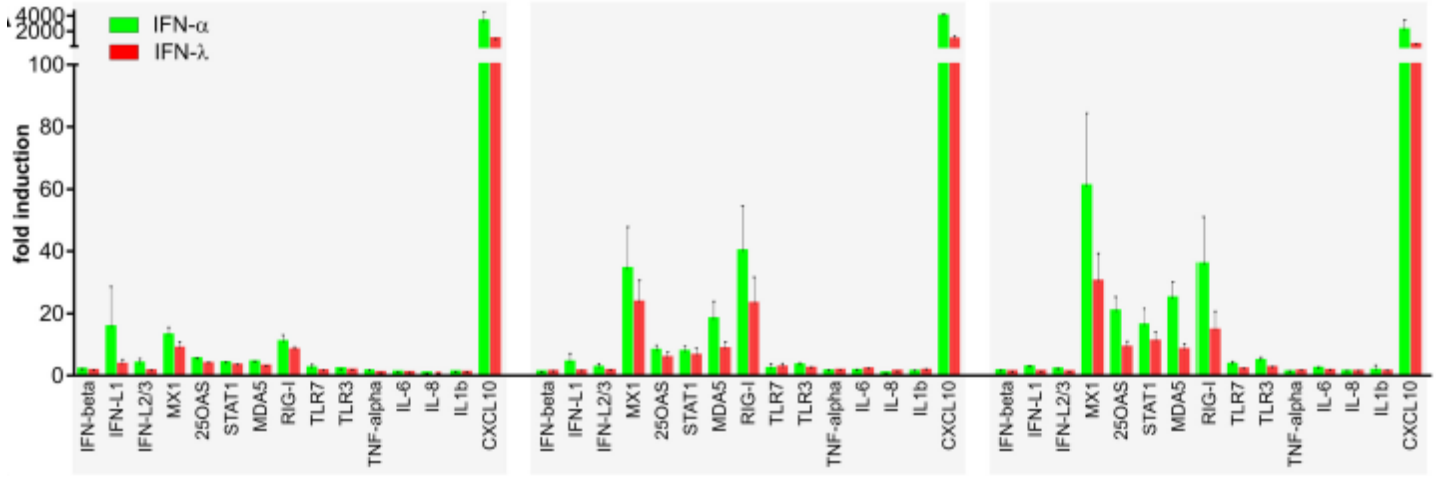
| | | | | | |
|---|---|---|---|---|---|
| **Interferon-alpha** | Not specified | Death: 1/96. Corticosteroids, human gamma globulin, interferon-a, and antiviral drugs may be some benefit in shortening clinical course | Clinical illness in patients (mostly hospital staff) is described but the effect of treatment cannot be evaluated. | Inconclusive | (4) |

# Efficient Replication of the Novel Human Betacoronavirus EMC on Primary Human Epithelium Highlights Its Zoonotic Potential

Only limited early transcriptional response to coronavirus infection




Respond swiftly to type I and type III IFN treatment with upregulation of ISG expression (i.e., Mx1, 2’-5’-OAS, Stat1, Mda5, Rig-I)

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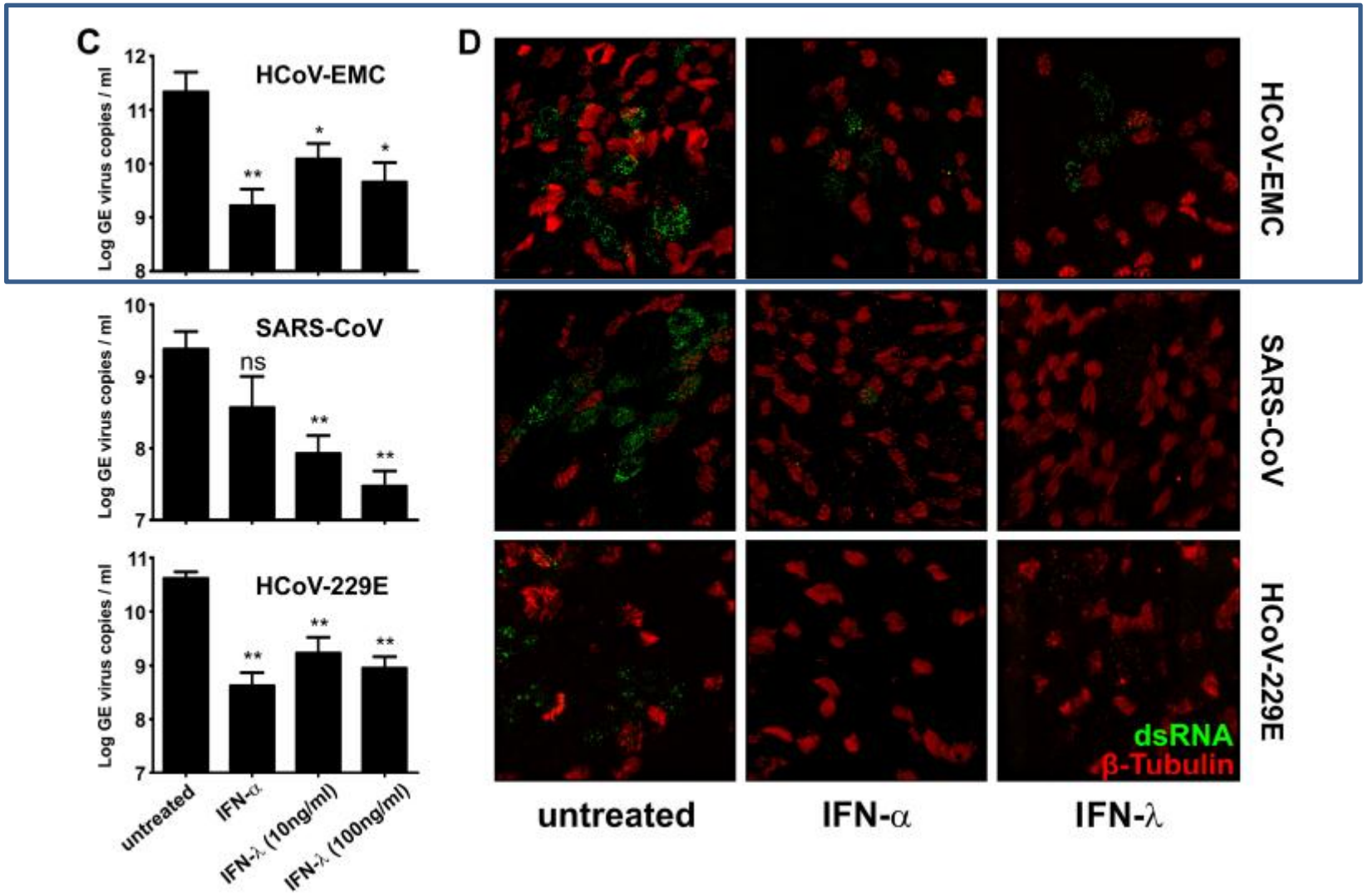


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# Efficient Replication of the Novel Human Betacoronavirus EMC on Primary Human Epithelium Highlights Its Zoonotic Potential

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E.K., H.R.J., and D.M. contributed equally to this work. R.D. and V.T. contributed equally to this work.

**ABSTRACT** The recent emergence of a novel human coronavirus (HCoV-EMC) in the Middle East raised considerable concerns, as it is associated with severe acute pneumonia, renal failure, and fatal outcome and thus resembles the clinical presentation of severe acute respiratory syndrome (SARS) observed in 2002 and 2003. Like SARS-CoV, HCoV-EMC is of zoonotic origin and closely related to bat coronaviruses. The human airway epithelium (HAE) represents the entry point and primary target tissue for respiratory viruses and is highly relevant for assessing the zoonotic potential of emerging respiratory viruses, such as HCoV-EMC. Here, we show that pseudostratified HAE cultures derived from different donors are highly permissive to HCoV-EMC infection, and by using reverse transcription (RT)-PCR and RNAseq data, we experimentally determined the identity of seven HCoV-EMC subgenomic mRNAs. Although the HAE cells were readily responsive to type I and type III interferon (IFN), we observed neither a pronounced inflammatory cytokine nor any detectable IFN responses following HCoV-EMC, SARS-CoV, or HCoV-229E infection, suggesting that innate immune evasion mechanisms and putative IFN antagonists of HCoV-EMC are operational in the new host. Importantly, however, we demonstrate that both type I and type III IFN can efficiently reduce HCoV-EMC replication in HAE cultures, providing a possible treatment option in cases of suspected HCoV-EMC infection.

**IMPORTANCE** A novel human coronavirus, HCoV-EMC, has recently been described to be associated with severe respiratory tract infection and fatalities, similar to severe acute respiratory syndrome (SARS) observed during the 2002-2003 epidemic. Closely related coronaviruses replicate in bats, suggesting that, like SARS-CoV, HCoV-EMC is of zoonotic origin. Since the animal reservoir and circumstances of zoonotic transmission are yet elusive, it is critically important to assess potential species barriers of HCoV-EMC infection. An important first barrier against invading respiratory pathogens is the epithelium, representing the entry point and primary target tissue of respiratory viruses. We show that human bronchial epithelia are highly susceptible to HCoV-EMC infection. Furthermore, HCoV-EMC, like other coronaviruses, evades innate immune recognition, reflected by the lack of interferon and minimal inflammatory cytokine expression following infection. Importantly, type I and type III interferon treatment can efficiently reduce HCoV-EMC replication in the human airway epithelium, providing a possible avenue for treatment of emerging virus infections.

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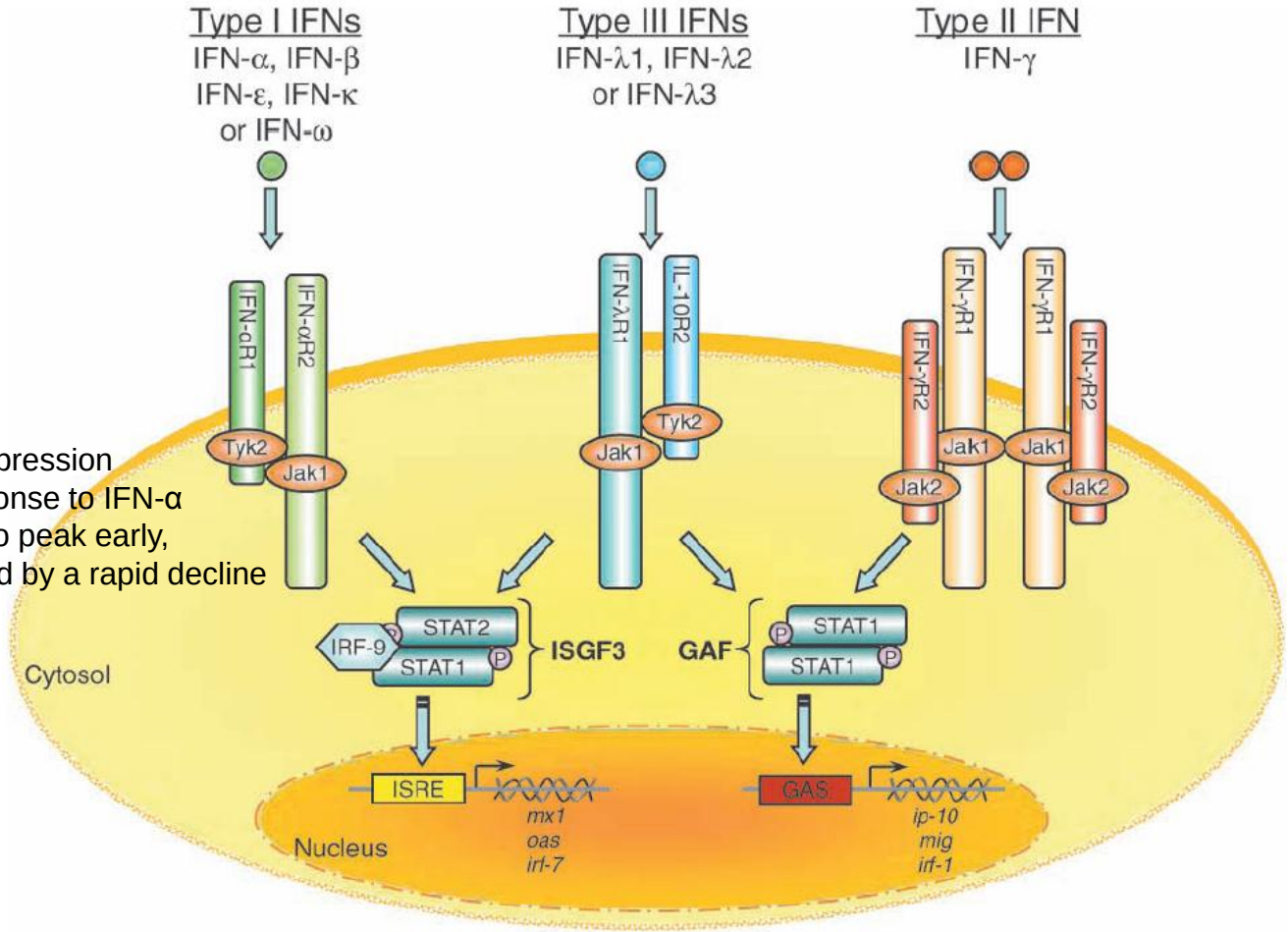
# Interferon – 3 types (I, II and III)

Viral infection / TLR agonist




ISG expression
in response to IFN-α
tends to peak early,
followed by a rapid decline

IFN-λ triggers a weaker
but more sustained increase
in ISG expression

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# Interferon

- Interferon α2a (Intron A)/α2b (Roferon-A)
  - 3 MU 3x/ week sc (based on dose for hepatitis)
- Pegylated interferon α2a (Pegasys)
  - 180 ug once weekly sc (based on dose for hepatitis)
- Pegylated interferon α2b (Peg-Intron)
  - 0.5-1.5 ug/kg once weekly sc (based on dose for hepatitis)

- Pegylated interfeon λ1a
  - 120, 180 or 240 ug once weekly sc (based on dose of hepatitis C phase IIb study)

# Interferon alfa – side effects

**General**

- Most patients experience dose-related side effects (more common with >18 million U).

**Common**

- Flu-like syndrome (50%–98%): fever, chills, fatigue, headache, arthralgias, usually within 6 hrs of administration, lasting 2–12 hrs. NSAIDs may alleviate Sx.
- GI intolerance (20%–65%): anorexia, abdominal pain, nausea, vomiting, diarrhea.
- Neuropsychiatric toxicity (20%–50%): irritability, depression, confusion, anxiety.
- Hepatitis (dose related in up to 40% receiving high doses).
- Marrow suppression.
- Rash and alopecia (up to 25%).
- Proteinuria.
- Metallic taste.

**Occasional**

- Dyspnea and cough.
- Elevations of bilirubin and alkaline phosphatase.
- Insomnia.
- Rash.

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# Interferon alfa – side effects and drug interactions

**Rare**

- Suicidal ideation or behavior.
- Thyroiditis with hyperthyroidism or hypothyroidism.
- Retinopathy.
- Rare cases of erythema multiforme, toxic epidermal necrolysis (TEN), and Stevens-Johnson syndrome reported.
- Injection site necrosis.
- Myositis.
- ITP and TTP.
- Decrease or loss of vision (case reports when used in combination with ribavirin).
- Reversible hearing loss and/or tinnitus.

**Drug Interactions**

- ACE inhibitors (captopril and enalapril): case reports of neutropenia and thrombocytopenia with coadministration. Monitor closely.
- AZT, ganciclovir, pyrimethamine, cancer chemotherapy, and 5-FC: additive bone marrow suppression with INF coadministration. Monitor CBC closely.
- Phenobarbital: phenobarbital serum levels may be increased. Monitor levels closely.
- Theophylline: theophylline serum levels may be increased. Monitor levels closely.

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# Potential experimental treatments

- Interferon α/ Interferon λ
- Protease inhibitor e.g. Lopinar/ritonavir
- Convalescent plasma

No specific treatment can be recommended

# Clinical management of suspected/confirmed case(s) of Novel Coronavirus

**Patient isolation and notification**

- Isolate the patient(s) in single room with Standard, Contact and Airborne precautions
- Notify via NDORS (if not yet done)

**Baseline investigation**

- Test of Novel Coronavirus
  - upper respiratory tract (NPA, NPS); lower respiratory tract (sputum, tracheal aspirate, BAL)
  - Paired serum (acute and convalescent)
- Other microbiological workup
  - Sputum, urine and blood culture
  - NPA for flu A/B and other respiratory viruses
  - NPA for atypical pneumonia PCR
  - Urine for Legionella antigen
  - Other tests as necessary
- CXR and ECG and other blood tests e.g. CBP D/C, L/RFT, RG, ESR, CRP etc

# Clinical management of suspected/confirmed case(s) of Novel Coronavirus

**Empirical antimicrobial agents**

- β-lactam/β-lactamase inhibitor combination OR 3rd gen ceph + macrolide
- Consider respiratory fluoroquinolone if allergy to β-lactam

**Monitoring and early recognition of complication(s)**

- Monitor vital signs and recognize complication(s) early
- Contact ICU early for intensive care if anticipate clinical deterioration

# Clinical management of suspected/confirmed case(s) of Novel Coronavirus

**Supportive treatment**

- Provide supportive treatment as necessary
  - Oxygen
  - IV fluid
  - Inotropic support +/- steroid* (shock)
  - Mechanical ventilation +/- ECMO (respiratory failure)
  - Renal dialysis (renal failure)

* Avoid high-dose systemic corticosteroids for viral pneumonitis; consider administration of intravenous hydrocortisone (up to 200 mg/day) or prednisolone (up to 75 mg/day) to patients with persistent shock who require escalating doses of vasopressors

# Clinical management of suspected/confirmed case(s) of Novel Coronavirus

**Specific treatment**

- Based on the current evidence, **NO** specific anti-viral treatment can be recommended at the moment
- *To be updated* in accordance to the latest research results and international guidelines

Thanks