

Editorial

The Plague (La Peste in French)

Urgent Recommendations

Five Don'ts to Prevent COVID-19 and Death

CONTENTS (April 2020, Vol. 6, No. 16)

Editorial

The Plague (La Peste in French)	2
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Urgent Recommendations

Five Don'ts to Prevent Novel Coronavirus Infection (COVID-19) and Death	3
1. Don't use ibuprofen or other NSAIDs	3
2. Don't use corticosteroids especially in the early phase of fever	8

Please read below in the next issue (No 17)

3. Don't use Tamiflu and Xofluza
4. Avoid ACE2 enhancers and (hidden) immunosuppressants
5. Don't sit up late at night. Lack of sleep is the strongest stress impairing your immunity

The Plague (La Peste in French)

Translated from the Editorial in Med Check (in Japanese) May 2020 ; 21 (51) ahead of print

The Plague is a masterpiece of Albert Camus (November 7, 1913-January 4, 1960), a novel written in 1947, shortly after the end of World War II. It predicts the status of the current world being swept by the pandemic of the novel coronavirus infection (COVID-19).

I read it for the first time when I was in the second grade of junior high school. It's been a long time, but a strange feeling after reading was completely different from other masterpieces I read in those days and has remained in my memory.

The second time I read it was during the harsh days after the Tokyo Electric Power Company's Fukushima Daiichi Nuclear Power Plant Accident following the Great East Japan Earthquake in March, 2011. I decided to read it again because I thought superposing the fear among people in Oran (port city in Algeria) attacked by the plague on the fear among people in Japan who were afraid of radiation would bring me mental stability. Nine years have passed since the accident (considering half-life of radioactive materials, this is still such a short time), and I have begun reading the novel again for the third time.

The following is taken from *The Pest* (translated from the Japanese edition by MIYAZAKI, Mineo). "My fellow citizens in Oran do a lot of work, but that is always to become rich." Isn't this similar to the current state of Japan, where people are so concerned about the impact of the new coronavirus on the Tokyo Olympics 2020, calling off of which would guarantee great financial loss? Camus also writes in the novel "Meantime, due to speculative intervention, daily necessities become scarce and are sold at unbelievable prices in the regular market." This reminds us of the shortage of masks in Japan, which are now sold online at unreasonable prices. In the end of the story, Dr. Rieux, who fought against the plague, says that in the life-or-death battle against the plague, humans were able to win because they had knowledge and memory. The fuss over COVID-19 will soon end, but it will be our responsibility to accurately record and remember what happened and to pass that knowledge on to the next generation.

Now that many events have been canceled and recreational facilities are closed, why don't you read *The Plague*? (KIMOTO, Yasusuke)

Urgent Recommendations

Five Don'ts to Prevent Novel Coronavirus Infection (COVID-19) and Death

Translated from [Med-Check News No.184 \(March 15 2020\)](#) with a little revision on March 25, 2020

Med Check Editorial Team

This article discusses 2 points of the 5 points which you should avoid to prevent novel corona virus infection (COVID-19) and death. The remaining three points will be discussed in the next issue. English version of Med Check News No. 183 that explained five points you should follow in details and No 185 will appear in the Med Check in English No 17 that will be published on around March 30.

Don'ts (Summary of 5 points)

1. Do not use antipyretics to lower fever. Human body can endure fever at 40-41°C . Because viruses are weak to heat, lowering fever with antipyretics will lead to regrowth of the viruses. In particular, non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided, because they also weaken your defense system. Acetaminophen (paracetamol) is basically harmful, as well.
2. Do not use corticosteroids for the same reason. Its use in the early phase of infection leads to higher mortality.
3. Do not use Tamiflu and Xofluza as they suppress immunity.
4. Avoid ACE inhibitor and ARB (angiotensin II receptor blocker) as possible, because they increase ACE2, an enzyme counteracting angiotensin II which act as a main receptor for SARS-CoV-2 to infect human. Apart from anticancer drugs, corticosteroids and overt immunosuppressants used for collagen diseases etc, there are many other drugs that reduce your immunity (hidden immunosuppressants) They include antihypertensive drugs especially ARBs and calcium antagonists, sleeping pills, anxiolytics, cholesterol lowering agents, antidiabetics (glitazons, DPP-4 inhibitors, GLP-1 agonists) and PPIs etc. They should be avoided unless they are essential.
5. Do not sit up late at night. A lack of sleep can be the strongest stress impairing your immunity.

Keywords:

COVID-19, ibuprofen, NSAIDs, paracetamol, corticosteroid, SARS-CoV, ACE-I, ARB, immunosuppressants, sleeping pills, glitazones
hidden-immunosuppressants

1. Do not lower fever with antipyretics

Summary

A human being as well as other animals can endure fever of 40-42 °C for 24 hours unless s/he has severe illness. As shown in Med Check News No. 183,

SARS virus and its surrogate viruses were inactivated at temperature 40 °C and relative humidity > 95% in 6 hours.

If you lower your high body temperature to near normal by using antipyretics and/or other physical

measures because you feel that you cannot endure fever, it takes longer to kill viruses and bacteria, and they might regrow and might make your body temperature higher than the initial temperature.

Especially, non-steroidal anti-inflammatory drugs (NSAIDs), such as aspirin, ibuprofen, diclofenac and mefenamate do not only lower fever, but also impair immunity, leading to aggravation of infection and increase mortality. They should never be used.

Acetaminophen (paracetamol) is less harmful than NSAIDs, but when it is used in high dose for lowering

fever to the normal temperature, it can aggravate infection. For instance, when it was used in children with chickenpox (varicella), the time to recovery was prolonged. Moreover, when it was used to lower fever to the normal temperature in serious infection such as sepsis, risk for death was increased by seven-fold in human.

Aspirin is considered to have relatively mild effect among NSAIDs. However, it is epidemiologically and medically established that it causes Reye syndrome, in which mainly children experienced encephalitis and liver damage after infection, which became an international issue in 1970's (risk is about 20 times higher).

Ibuprofen is generally believed to be less harmful than diclofenac and mefenamate. However, it aggravates infection in human and increases mortality when used in critically ill patients with infection as well as in infected animals. Mortality risk is 7 times higher for human and about 20 times higher in infected animals. Do not use any antipyretics.

(1) Infected animals did not die at 42°C, but 3/4 of them died at 34°C

Figure 1 shows the comparison of mortality in lizards which were infected with bacteria and placed in rooms at 34°C, 36°C, 38°C, 40°C or 42°C [1]. Comparison was made in this way because reptiles can hardly increase

their body temperature.

At any points of days 1, 2 and 3, and one week, lower temperature was associated with higher mortality. Likewise as the temperature increased, mortality was decreased. After 24 hours, three-fourths (9 /12), two-thirds (8/12) and half (18/36) of the animals died at 34 °C , 36 °C , 38 °C , respectively. However at 40 °C , only one-sevenths (2/14) died and at 42°C there was no death. After 3.5 days, mortality at each temperature was 100%, 75%, 70%, 33% and 8%, respectively. After one week at 42°C , the mortality increased to 25%. However, considering that 34% of uninfected animals died at 42°C after one week. It can be said that at 42°C , the animals died not from infection but from high temperature.

This suggests that having fever of 42°C for many days is risky, but it can be endured for one day. Moreover, at 42°C , infection is not the cause of death.

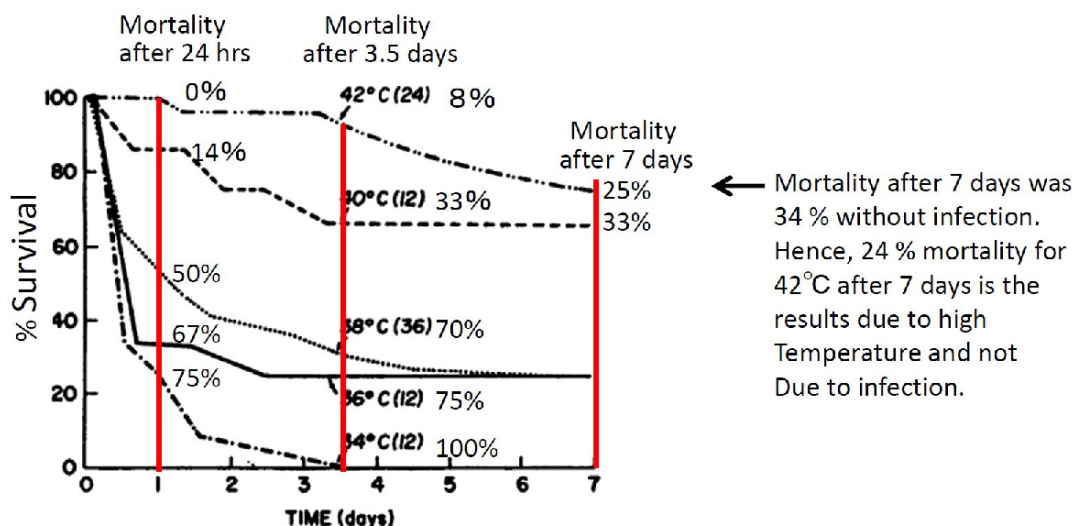
In reality, body temperature does not increase higher than 41°C in infection. Rather, it tends to become higher when it recurs after once lowered with antipyretics.

(2) Strong antipyretics aggravate infection and increase mortality by 10 to 20 folds.

A highly fatal disease, in which infection such as influenza or chickenpox was followed by encephalitis

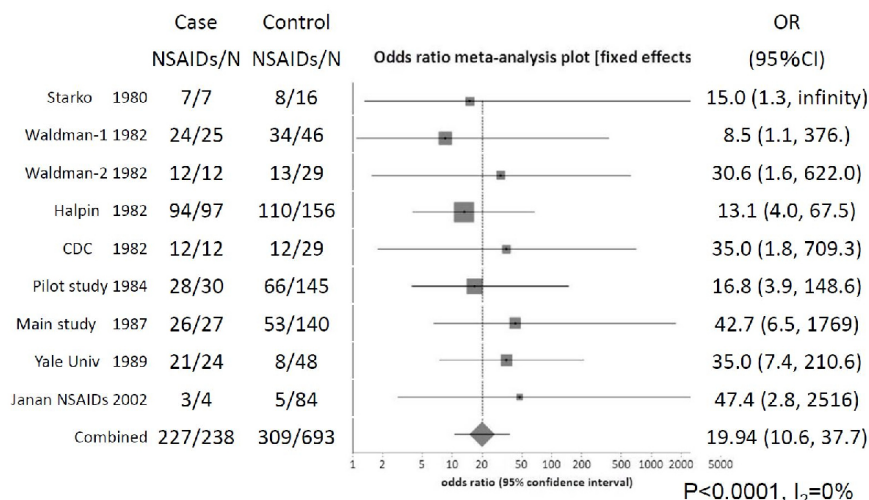
Figure 1: Should fever of 40°C and above be lowered?

No: Fever of 42°C can be endured for 24 hours. If not lowered, infection can be cured faster.



Cited from ref [1]

Figure 2: NSAIDs such as aspirin or diclofenac increase death from Reye's syndrome/influenza encephalitis by 20-folds (meta-analysis of case-control studies in the U.S. and Japan)



Pooled odds ratio by Fixed effects (conditional maximum likelihood) = **25.61** (13.0, 55.7), P< 0.0001

Japan: A case-control study of influenza associated encephalopathy comparing use of NSAIDs including diclofenac and mefenamate. Others: all are case-control studies for Reye's syndrome conducted in US. .

and liver damage, was reported in 1960's. This condition was named after a doctor who found it and is called Reye Syndrome. It was intensively studied around 1980, and it was found that aspirin was the cause and increased the risk of the syndrome by about 20-folds (Figure 2). They stopped using aspirin in the West and no Reye syndrome case has occurred since then [2].

In Japan, aspirin has been rarely used. However, syndrome of acute encephalopathy of unknown cause with multi-organ failures after common cold or influenza in which patients deteriorated much more rapidly than Reye's syndrome, became an issue. It was later investigated as influenza associated encephalopathy but the syndrome is not only associated with influenza

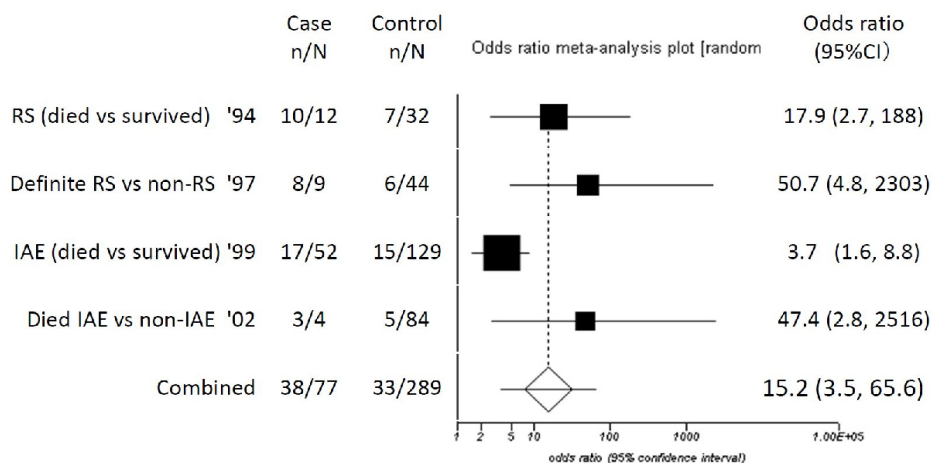
but also with other mild infections like common cold or varicella. In Japan, instead of aspirin, antipyretics with stronger anti-inflammatory action had been used.

These non-steroidal anti-inflammatory drugs (NSAIDs) included diclofenac, mefenamic acid (mefenamate). Many studies were conducted by a task force of Japan's Ministry of Health and Welfare (MHW before 2000). Quasi case-control

studies using the case series of acute encephalopathy of unknown cause until '97 showed that the NSAIDs increased the risk of encephalitis by 26-folds (Figure 3). However, Japanese government did not admit it before the study in 1999.

As a result of banning the use of these antipyretics in children, proportion of death from encephalopathy following mild infections including influenza has rapidly decreased (30% to less than 10%, data not shown). Currently, only acetaminophen is used as an antipyretic in children and in most adults as well in Japan. However, after the introduction of Tamiflu again increased death related to influenza.

Figure 3: Meta-analysis of Japanese studies on encephalopathy and NSAIDs



RS: Reye's Syndrome, IAE: influenza associated encephalopathy The study '02 was only a case-control study. Others were all quasi case-control studies using case series of infection associated encephalopathy or Reye's syndrome. NSAID use in influenza increases risk of death from IAE or RS by about 15 times compared with no use of NSAIDs as antipyretics. Data by 1997 showed risk increase by 26 times already (Combined odds ratio of studies '94 and '97 =26.5(5.8,103), p<0.0001)

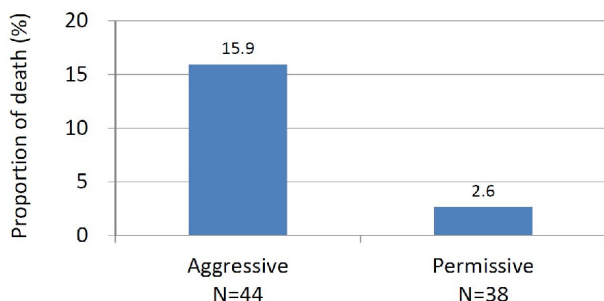
(3) Acetaminophen may also increase mortality when it is actively used.

Currently, acetaminophen (paracetamol) is considered to be the safest among antipyretics, compared with many NSAIDs including aspirin. It is correct. However, it is not true that it has no harm in increasing death.

In many countries including Japan, according to the label, 40mg/kg/day (maximum 60mg/kg/day) is allowed to use in children with fever. This dose, 40mg/kg/day, was used in children with chickenpox for 4 days. It prolonged the time to total scabbing by 1.1 days as compared with placebo (p=0.048) [5].

There is a study involving critically ill adult patients staying at ICU longer than 72h with body temperature of >38.5 degree C [6]. They were randomized into aggressive or permissive groups. The aggressive group received acetaminophen 650 mg every 6 h for temperature of >38.5 degrees C and a cooling blanket was added for temperature of >39.5 degrees C. The permissive group received no treatment for temperature at 40 degrees C or less, but instead had treatment initiated at temperature of >40 degrees C, at which time acetaminophen and cooling blankets were used until temperature decrease less than 40 degrees C. While in the permissive group, only 2.6% of the patients (1/38) died, 16% of the patients (7/44) died in the aggressive group (odds ratio=7.0, p=0.06 by Fisher's exact test) (Figure

Figure 4: Adverse effect of antipyretic therapy upon outcome of critically ill patients: randomized prospective study



Data from ref [6].

Aggressive: acetaminophen 650mg, 6 hourly if BT>38.5 °C to reduce BT<38.5°C

+ cooling blanket when >39.5°C to reduce BT<38.5°C .

Permissive: same dose if BT>40 °C to reduce BT <40 °C . The study was stopped after the first interim analysis due to the mortality difference (OR=7.0, p=0.06 by Fisher's exact test).

4). This suggests that even acetaminophen increases mortality by 7-folds when it is used to lower fever aggressively to the near normal temperature.

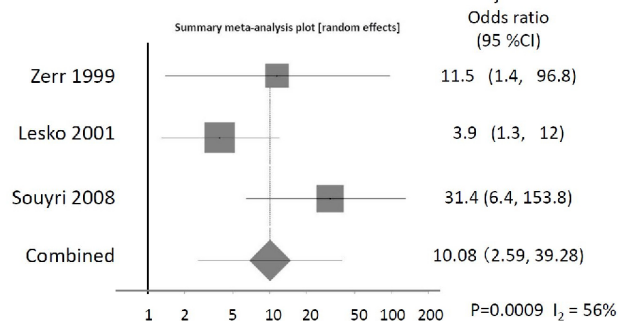
(4) Ibuprofen also aggravates infection

Ibuprofen is considered to be the mildest among NSAIDs, and is marketed as OTC antipyretics and commonly used in Western countries. In Japan, the daily dosage for adults is 600 mg. However, in the U.S., one tablet (of even OTC drug) contains 400 mg or 600 mg of ibuprofen, and is purchased without prescription.

The safety of ibuprofen is claimed based on the two large-scale controlled studies [3,4] showing that there was no difference in safety between ibuprofen and acetaminophen. However, it is harmful to use acetaminophen to lower temperature as shown in above RCTs [5,6]. Therefore, it may be true that ibuprofen also aggravates infection.

This is actually shown in some studies. Chickenpox is sometimes complicated with bacterial infection, leading to severe bacterial infection in subcutaneous tissues, such as necrotizing fasciitis. We found three case-control studies that examined the association between the complication of varicella and use of NSAIDs antipyretics, including ibuprofen [7-9]. As a result of meta-analyzing these studies, it was concluded that ibuprofen use is associated with increased severe infection of varicella by 10-folds (p=0.0009) (Figure 5).

Figure 5: Ibuprofen* increases sever complication ** of human by 10 times (meta-analysis of three case-control studies)



* : Souyri's study [9] include other NSAIDs than ibuprofen.

** : Cased were all severe soft tissue infection after varicella including necrotizing fasciculitis.

Meta-analysis results of three studies: Zerr 1999 [7], Lesko 2001 [8], Souyri [9]

(5) Mortality risk of NSAIDs is well proven by many infected animal studies

There are numerous kinds of infected animal studies which equivocally indicate that NSAIDs increased mortality of infected animals. Animals used include mice, rats, rabbits, chickens and goats etc. and microbial include bacteria, viruses and protozoa etc. NSAIDs include aspirin, mefenamates, ibuprofen, indomethacin and flurbiprofen etc. Acetaminophen is also tested in some studies

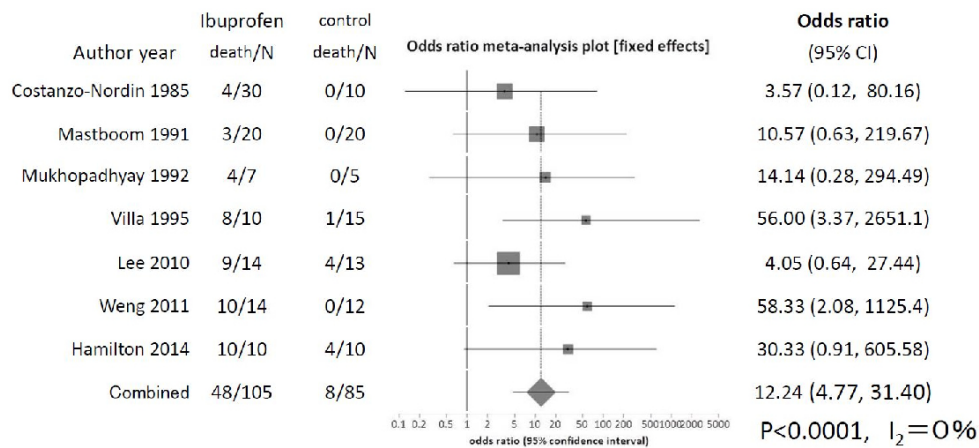
So far until March 13, 2020, we got data from 25 experiments that compared the mortality rate between NSAIDs group and the vehicle group. A meta-analysis

showed that NSAIDs antipyretics increased deaths of infected animals by about 15 folds.

Figure 6 shows the results of a meta-analysis of the risk when ibuprofen is used for infectious diseases in various animals. Infected microbial includes influenza virus, bacteria from cecal ligation and puncture. Ibuprofen has been shown to increase the deaths of infected animals by 22 folds compared to vehicle only without NSAIDs.

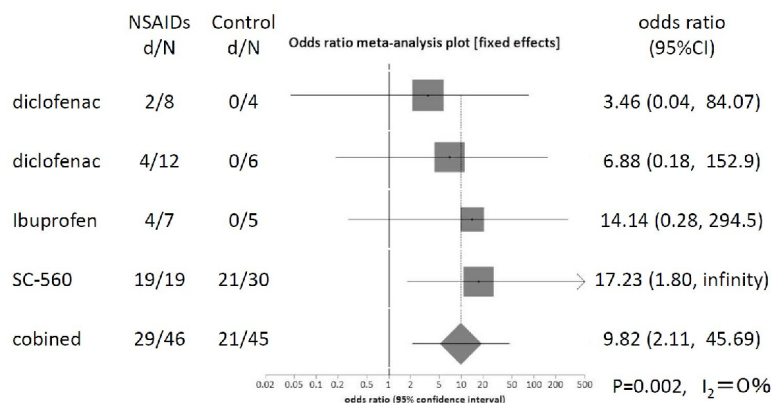
Figure 7 is the meta-analysis results of four influenza infected animal studies showing that NSAIDs increased

Figure 6: Ibuprofen increases mortality of infected animals by 20-folds



Pooled odds ratio (Fixed effects, conditional maximum likelihood)= 22.2 (95% CI=7.3, 84.6), P<0.0001
 Infected microbial includes influenza virus, bacteria from cecal ligation and puncture.

Figure 7: NSAIDs increased mortality of influenza-infected animals at least by 10-fold (meta-analysis results)



Pooled odds ratio (Fixed effects, conditional maximum likelihood) = infinity (3.75, infinity), P < 0.0001
 Study of Ibuprofen is the same as the study by Mukhopadhyay 1992 in Figure 6.

risk of mortality from influenza infection at least by 10 folds: Pooled odds ratio is infinity (95%CI: 3.75, infinity, p<0.0001) by fixed effects, conditional maximum likelihood method (references are not shown).

(6) The risk from NSAIDs use in humans and in other animals is similar

In humans, Aspirin or NSAIDs antipyretics increased risk of Reye's syndrome and influenza associated encephalopathy by 20 times, ibuprofen increased severe varicella infections by 10 times, and even acetaminophen increased mortality by 7 times when used in order to lower fever aggressively as mentioned in the section (3).

In infected animals as shown in the previous section (5), NSAIDs increased mortality by 10 to 20 times.

Thus, the level of increased risk of mortality or exacerbation of human infections and increased mortality of infected animals are indeed in good agreement.

Therefore, not only NSAIDs antipyretics, but also acetaminophen worsens infection if used aggressively for lowering to near normal temperature.

It is extremely harmful to use antipyretic agents for reduction of fever in the novel coronavirus infection.

Never use NSAIDs including ibuprofen in the novel coronavirus infection (COVID-19).

Don't use acetaminophen/paracetamol to lower temperature aggressively.

2. Do not use corticosteroids especially in the early phase of fever

Summary

NSAIDs make infections more severe if used to reduce fever. If corticosteroid is used instead of NSAIDs it also worsens infection. Human and animal studies have equivocally shown that the earlier the corticosteroid is used, the more severe the infection and the higher the mortality rate become. Let's take a closer look.

(1) Severe or increased death when used early in the onset of influenza

A study [10] was conducted on the 2009/10 influenza (so called pH1N1 infection), suspecting a relationship between the severity of the influenza and the early use of corticosteroids. In China primary care practitioners use them as antipyretics, potentially exposing hundreds of millions to this risk [10], while it is rarely prescribed by doctors for influenza in Japan.

The purpose of this study [10] was to determine whether the use of corticosteroids in the early stage of influenza (onset within 72 hours = 3 days) or late (after 72 hours) had increase severity and/or death from influenza compared with never use of corticosteroids. As a result, it was found that using corticosteroids early increases the severity of the disease, including death, by 6.5 times (Table 1).

The study also indicated that the late use of corticosteroids (after 3 days) is associated with 3-folds increase of severity or death from influenza infection [10].

Ma et al reported that glucocorticoid and pyrazolone use as antipyretics is associated with life-threatening

Table1: Early use of corticosteroids increased severity or mortality by 6.5 times

Corticosteroid use and its timing		N	critical/death		crude OR (95%CI) p value	Risk ratio		hazard ratio
			n	%		crude	adjusted	
Corticosteroid use	early	17	12	70.6	6.5 (1.8, 23.1) p=0.002	2.6 (1.4, 4.8)	3.3	2.9 (1.3, 6.2)
	late	29	16	55.2	3.3(1.2, 9.3) P=0.020	2.0 (1.1, 3.8)	2.1	
	never	37	10	27.0	reference	reference	reference	reference

Early: Use within 72 hours of onset, Late: Use after 72 hours of onset. This study is quasi-case-control study, hence odds ratio should be used for risk analysis. Note that levels of adjusted risk ratio or hazard ratio are larger than crude ratio. Hence, crude odds ratio may be underestimated for the true risk of early corticosteroid use.

Table2: Antipyretic use and serious complication from EV71 infection.

Use of antipyretics (corticosteroid or pyrazolone)	Case N=28		Control N=40		OR (95%CI)	P value
	N	%	N	%		
Parenteral antipyretic	22	63.6	35	20.0	7.0 (1.8, 28)	0.002
Corticosteroid	20	75.0	31	38.7	4.8 (1.2, 21)	0.021
pyrazolone	19	42.1	33	15.2	4.1 (0.91, 19)	0.047
Both/none	9	77.8	14	2.0	21 (1.8, 305)	0.007

Numbers of denominators are different because unknown users were excluded. Numbers of denominators for Both/none were the sum of both and non-users. From the data by Ma et al [11].

human enterovirus 71 (**EV71**) infection during an outbreak in China [11]. They say “About 50% of the 28 cases and 18% of the 40 controls received an **injection** to treat fever during the first 96 hours after onset (**Odds ratio =7.0**, 95% confidence interval: 1.8 –28). Injections containing exclusively **glucocorticoids** (**OR = 4.8**, 95% CI: 1.2-21) or **pyrazolones** (**OR = 4.1**, 95% CI: 0.91-19, P= 0.047) were risk factors for severe HEV71 infection. About 25% of cases and 5% of controls received **both drugs parenterally** while 7% of cases and 30% of controls received neither (**OR = 21**, 95% CI: 1.8-305). Conversely, cases and controls had identical average initial temperature, and did not differ significantly by age, sex, nutritional measurements, use of other drugs, or timeliness of medical care received.” Table 2 summarizes the results by Ma et al (Table 2).

Ma et al discussed “In general, **dexamethasone was more commonly given early in the course of the illness** and methyl prednisolone later. We did not detect a similar time trend with pyrazolones. We were not able to retrieve the actual dose of glucocorticoids or pyrazolones given to these patients but **it was common practice to administer up to 50 mg of dexamethasone and up to 550 mg of aminopyrine for fever reduction.**” [11]

These data strongly indicate that use of corticosteroids especially combined with NSAIDs antipyretics at the early phase of mild infection leads to deterioration of otherwise mild infection.

There are relatively many observational studies on whether corticosteroid use for serious infection is related to the increased mortality. In these cases, it is difficult to determine whether the corticosteroid was used due to the severity of the disease or it caused the infection

serious unless time related bias is well controlled [12]. However, these studies [10, 11] examined corticosteroids used in the early stages of onset when the infection was not severe. Hence they have least time related bias.

In addition, animal studies [13] have shown that the use of corticosteroids one day after inoculation of virus showed the highest mortality, as described later.

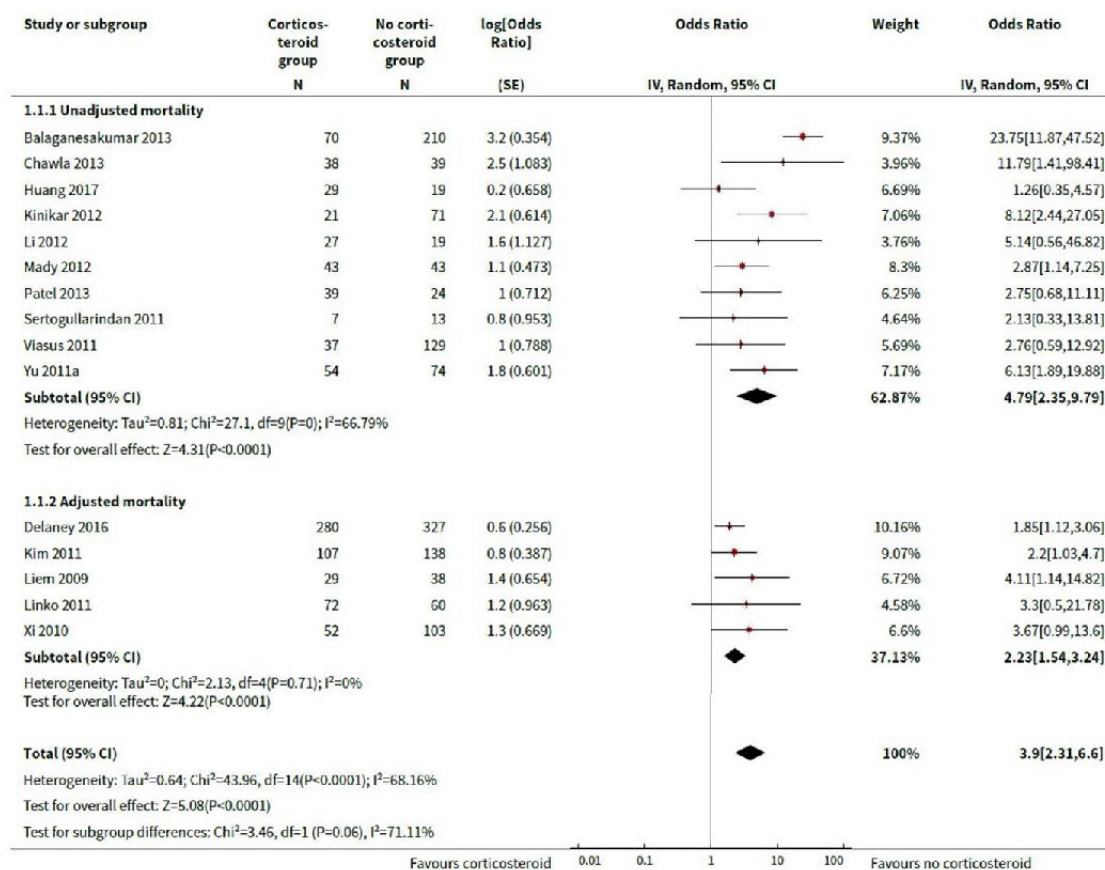
At the early phase of infection especially just after the start of fever, you have to concentrate on fighting to reduce virus by utilizing your whole defense system including fever and other immune functions. At that time, if your body temperature is reduced by corticosteroids and/or NSAIDs antipyretic, your defense system including immune response as well as inflammatory response are suppressed, the virus will not be destroyed and may increase and enter deep into your body and induce more cytokines to fight against increased viruses leading to cytokine storm and multi-organ failure. Considering the mechanism of action of corticosteroids, the results in humans and animal experiments described later is quite reasonable.

(2) Corticosteroid treatment for patients with severe influenza increases death

Corticosteroids are often used when a patient with influenza become seriously ill and hospitalized especially admitted to ICU. The systematic review and meta-analysis of observational studies reporting the risk of death with corticosteroid use for hospitalized patients with influenza [16] indicate the risk was 4.8 times higher (Figure 8).

It is difficult to judge whether the mortality rate has increased due to the severity of the disease or the use

Figure 8: Adverse effect of corticosteroid therapy on death in influenza inpatients



et al. Corticosteroids as adjunctive therapy in the treatment of influenza. *Cochrane Database of Systematic Reviews* 2019, Issue 2. Art.No.: CD010406.

Cited from Ref. [16]

of corticosteroids. However, combined odds ratio by adjusting timing of corticosteroid use was 2.23. Hence, it can be said that corticosteroid use increases the mortality (Figure 8).

(3) Even with septic shock, high dose corticosteroids are harmful

Pulse treatment using large doses (1000 mg/day) of methylprednisolone for 3 days which is commonly used for septic shock is also harmful. The Japanese label of methylprednisolone warns “there is a report [15] indicating that high dose of this drug increased mortality in patients with septic shock with high creatinine level (> 2.0 mg/dL)”.

Another Cochrane review [16] reported that in patients with septic shock, corticosteroids equivalent to 200mg/day of hydrocortisone reduced deaths up to 28 days after hospitalization. However the mortality was not different after 6 month.

In conclusion, even for septic shock, corticosteroids

use had little meaning and early use of corticosteroids for mild infection worsens the infection.

(4) The earlier a corticosteroid is used, the greater the risk of death becomes: Results of Animal studies

Experiments with infected animals have confirmed that corticosteroids use for infection increases mortality. Moreover, it has been confirmed that the earlier the infection, the greater the mortality rate becomes [13].

Enterovirus 71 (EV71) is a causative virus of hand, foot, and mouth disease (HFMD) or herpangina. These infections are usually mild but sporadic cases of neurologic disease or outbreaks of severe, life threatening disease including encephalitis, acute respiratory failure and excess mortality were reported in the Asia-Pacific region including China [10,11,13] where 353 severe cases of HFMD and 22 fatalities out of over 6000 cases were reported in Fuyang in 2008 [17].

In severe cases, corticosteroids are often used to relieve cytokine storms (Note). However, a series of

Note: When infected with the virus, the body produces various chemicals called cytokines such as interferon and tumor necrosis factor, along with high temperature, to fight the virus. When the amount of virus increases, it becomes necessary to release many cytokines. When the amount of virus increases extremely, the cytokine comes out like a storm and attacks the virus. However, not only viruses but also body cells are attacked and damaged. Antipyretics and corticosteroids do not kill the virus, but rather the virus needs to produce more cytokines for the virus to multiply, resulting in a cytokine storm.

disease severity of mice infected with enterovirus 71 (EV71) compared with those treated with saline (phosphate buffer saline: PBS) [13]. However, EV71 infected mice with corticosteroids treatment starting from 1 day post-infection died one after another (Figure 9).

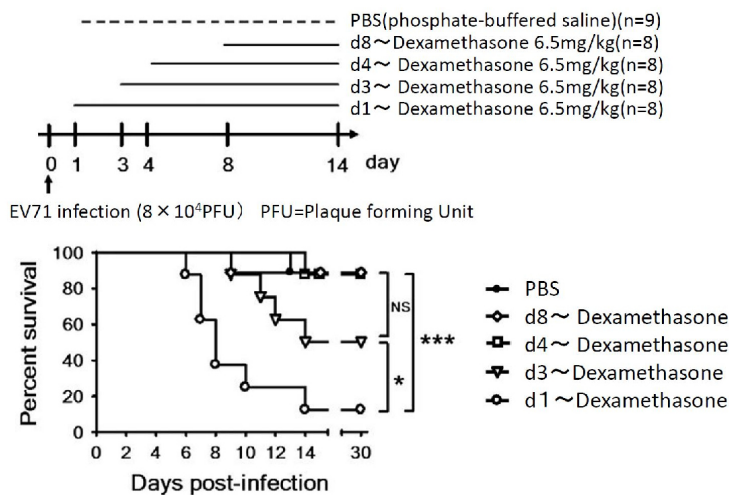
Mortality of severely infected mice with 6×10^5 PFU/mouse of EV71 increased even with PBS, but all with corticosteroid treatment starting one day post-infection died on the ninth day (Figure10).

infected animal studies were conducted on suspicions that corticosteroids might worsen the symptoms of infection [13]. Figure 9 ~11 shows some results of these studies.

Meta-analysis of the three experiments showed that corticosteroids starting from one day post-infection increased the risk of death by 70-fold compared to PBS (Figure 11). Pooled odds ratio by the conditional maximum likelihood (Fixed effects) was 70.8 (95%CI:7.6, 3880, < 0.0001 , $I^2 = 0\%$)

Corticosteroid (dexamethazone) treatment starting from 4 or 8 days post-infection did not affect mortality and

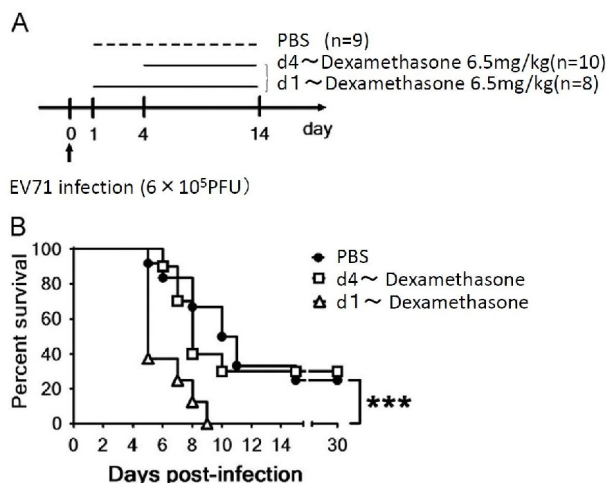
Figure 9: The mortality risk increases with early use of corticosteroids (1)



The survival rates of mice were compared when dexamethasone was started 1, 3, 4, and 8 days post-infection of enterovirus 71 (EV71) and control mice treated with saline (phosphate buffer saline: PBS) starting 1 day post-infection. The greatest risk of death was observed when corticosteroids were started 1 day post-infection. .

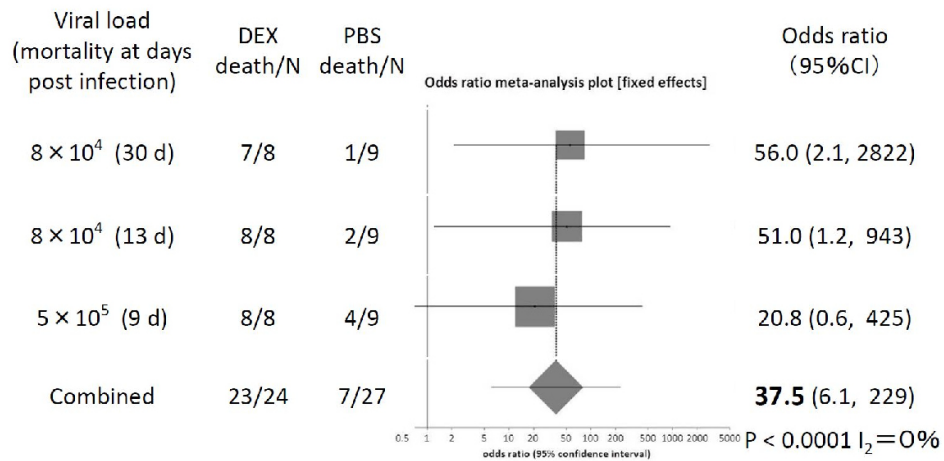
From ref. [13]

Figure10: The mortality risk increases with early use of corticosteroids (2) Infected with high doses of virus



From ref. [13]

Figure 11: Starting corticosteroids on 1 day post-infection increases mortality of mice infected with EV71 by 70 folds



Viral load is expressed as PFU (plaque forming unit); Meta-analysis results of three experiments in Ref. [15]; Pooled odds ratio by conditional maximum likelihood (Fixed effects) = **70.8** (95% CI: 7.6, 3880), P <0.0001

Details for the following 3 Don'ts will be explained with evidence in the next issue of Med Check in English No.17

3. Do not use Tamiflu and Xofluza as they suppress immunity.

4. Avoid ACE inhibitor and ARB (angiotensin II receptor blocker) as possible, because they increase ACE2, an enzyme counteracting angiotensin II which act as a main receptor for SARS-CoV-2 to infect human. Apart from anticancer drugs, corticosteroids and overt immunosuppressants used for collagen diseases etc, there are many other drugs that reduce your immunity (hidden immunosuppressants)

They include antihypertensive drugs especially ARBs and calcium antagonists, sleeping pills, anxiolytics, cholesterol lowering agents, antidiabetics (glitazons, DPP-4 inhibitors, GLP-1 agonists) and PPIs etc. They should be avoided unless they are essential.

5. Do not sit up late at night. A lack of sleep can be the biggest cause of stress that impairs your immunity.

Details for the following 5 Do's will also be described with evidence in Med Check in English No.17

1. Simple mask-wearing is effective. It reduced illness from SARS to one-third, and is more effective than frequent hand-washing (>10/day) that halved it.

2. Mask-wearing is effective because SARS-CoV is vulnerable to high temperature with humidity. It helps your nose and throat keep warm and moisturized.

3. When masks are not available, make it with cloths or handkerchief. They can be washed and used repeatedly.

4. Drink hot drinks such as "kuzuyu (drink made from arrowroot starch). Blowing on and sipping it help warm the throat and the whole body.

5. Get moderate exercise during the day, and have enough sleep at night, but without sleeping pills.

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