

# Rational prescribing for upper respiratory tract infections (URTI)\*

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## Summary

*Upper respiratory tract infections (URTI) are the most common illnesses encountered in family medicine. Prescribing for this condition has a great health and economic impact. This paper critically appraises the rationale behind the prescribing of different drugs for URTI. Over 90% of URTI are self-limiting and are caused by viruses that do not require any curative treatment. Research data show that curative treatment is available for only the very small proportion of URTI that are caused by influenza viruses or bacteria, and the benefit is modest. Many drugs advocated for the relief of URTI symptoms lack support from research evidence. There is no justification for the use of steroids or non-steroidal anti-inflammatory drugs (NSAID) because their benefits are doubtful and their side effects can be serious. Apart from influenza vaccine for the prevention of influenza, no drug has been fully proven to be effective in preventing URTI or its complications. Local studies have shown that not all patients expect a pill for every ill and some patients think the doctor gives too many drugs. A careful analysis of the nature and severity of the patient's symptoms can lead to the rational prescribing of the least number of the most needed drugs.*

## 摘要

上呼吸道感染是最常見的疾病，其用藥對健康和經濟都有巨大的影響。本文討論上呼吸道感染藥物處方的原則。九成以上的上呼吸道感染是由過濾性病毒

所引起，無需用藥亦可痊癒。研究證明治療性用藥只可促進少部份由細菌或流行性感病毒引起的上呼吸道感染的痊癒，而效益只是一般。很多聲稱能減輕上呼吸道感染引致的症狀的藥物並沒有足夠的証據。使用類固醇或非類固醇消炎止痛藥 (NSAID) 治療上呼吸道感染並不適合，不但療效成疑，而且可能引起嚴重的副作用。除了流行性感疫苗之外，沒有足夠證據顯示其他藥物可以有效地預防上呼吸道感染或其併發症。研究發現本地病人並非期望每個病都要藥物治療，有些人還認為醫生處方的藥物數目過多。如醫生能小心分析病情，就能理性地處方最少而且最有效的藥物。

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## Why do doctors prescribe?

A 25 years old previously healthy lady consulted me for stomach pain after taking the drugs prescribed to her by a doctor she had consulted the previous day for an upper respiratory tract infection (URTI). Her five medications were labelled as prednisolone 5mg t.d.s., ciprofloxacin 250 mg daily, codeine phosphate 30mg t.d.s., phensedyl 10 ml t.d.s. and debrexan 1 tablet t.d.s. I told her to stop all the medications and that her URTI and stomach pain would subside without any drugs within a couple of days. I did not know what to say when she asked me why the previous doctor prescribed her so many drugs if none was necessary!

The Oxford Dictionary states that prescribing means "advise or order the use of medicine... the prescription of drugs is a doctor's responsibility".<sup>1</sup> Society has empowered doctors with the privilege to prescribe potentially poisonous substances labelled as drugs because it trusts that doctors will bear the responsibility of using this power rationally. Rational prescribing means that each drug is given for a good reason and after the benefits have been balanced against the possible harm. A drug may be prescribed for the cure of a disease, to

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relieve symptoms or to prevent complications. It is controversial whether a drug should be given only to satisfy the patient's expectation.

URTI is a collective term for infections of part or whole of the upper respiratory tract that spans from the nose to the larynx. They can be caused by a wide variety of organisms.<sup>2</sup> The common cold (coryza) is the most common URTI, it is always caused by a virus, the commonest being rhinovirus.<sup>3</sup> Influenza refers to URTI caused by an influenza virus and clinically can be differentiated from other URTI by the presence of high fever (>38°C) with dry cough and sore throat, severe systemic upset with myalgia and relatively mild nasal symptoms. Pharyngitis and tonsillitis can be caused by a virus (70-90%) or bacteria (10-30%).<sup>4</sup> Acute epiglottitis caused by haemophilus influenza is very rare but potentially dangerous. Acute laryngitis, typically presenting with hoarseness, is more commonly caused by a virus than bacteria. Treatment for URTI should be guided by the pathological diagnosis and be evidence-based.

### Curative treatments for URTI

The majority of URTI are self-limiting viral infections that can be cured by our own immune system without any drug. A curative treatment needs to be able to hasten recovery in order to be considered effective.

### Antibiotics

Antibiotics are probably the most commonly used curative treatment for URTI, although less than 10% of cases are caused by bacteria. Two systematic reviews on a total of 19 trials failed to show any beneficial effect from antibiotics for the cure or symptomatic relief of the common cold, but the treatment groups reported more side effects.<sup>5,6</sup> Antibiotics may increase the cure rate of rhinosinusitis characterised by persistent (more than 10 days) nasal discharge in children. Six children need to be treated in order to cure one child.<sup>7</sup> Antibiotics are commonly prescribed for patients with a sore throat but they confer no benefit to the majority of patients who do not have a bacterial infection.<sup>8,9</sup> Dagnelie *et al* showed that penicillin V could shorten the duration of pharyngitis by 1 to 2 days only in patients whose throat swab was culture-positive for group A beta haemolytic streptococci.<sup>8</sup>

The choice of antibiotics should be guided by epidemiological data on the likely pathogens causing the infection. Group A beta haemolytic streptococci are by far the most common bacterial cause of acute pharyngotonsillitis.<sup>4,10</sup> Group C and group D streptococci are sometimes found on throat swab cultures but they are of doubtful significance because they are often commensals of the respiratory tract.<sup>4</sup> Penicillin V is the most rational choice of antibiotic for a bacterial pharyngotonsillitis because Group A beta haemolytic streptococci are 100% sensitive to penicillin.<sup>4,10</sup> Erythromycin is often recommended as the alternative for patients who are sensitive to penicillin but as many as 22% of the group A beta haemolytic streptococci are resistant to this antibiotic.<sup>10</sup> A first or second generation cephalosporin may be a more effective choice but it runs the risk of 10% cross-sensitivity with penicillin.<sup>11</sup> There is little justification for the use of a third generation cephalosporin, which is less effective against gram positive organisms, more expensive and more liable to breed bacterial resistance.<sup>4,11</sup> Amoxicillin is still the first drug of choice for bacterial rhinosinusitis that is usually caused by haemophilus influenza or streptococcus pneumoniae, a second generation cephalosporin is a reasonable alternative.

The modest benefit of antibiotics in URTI should be balanced against their side effects, which can occur in an excess of 5% to 21% of the treated patients as compared with the placebo groups.<sup>12</sup> Over-prescribing of antibiotics encourages the development of resistance as evidenced by a correlation between the volume of antibiotics used and resistance rate within a population.<sup>13,14</sup> This is especially liable to occur with broad-spectrum antibiotics such as the macrolides and quinolones, which should be reserved for infections that cannot be cured by other antibiotics.

### Anti-influenza drugs

Randomised placebo controlled trials have shown that amantadine, rimantadine, oseltamivir and zanamivir can shorten the duration of influenza infections by about one day when the drugs are given within 48 hours of the onset of the illness.<sup>15</sup> It is important to note that amantadine and rimantadine are effective against influenza A only and none of the drugs are effective against non-influenza URTI. The subjects in these trials were usually previously healthy adults and most of them were below the age of 65, so the results may not be

applicable to children, the elderly and people with chronic diseases. The evidence on side-effects of these anti-influenza drugs is inconclusive. Amantadine and rimantadine have been associated with central nervous and gastrointestinal side effects. Inhaled zanamivir could cause bronchospasm and should be used with caution in people with chronic respiratory diseases.

Influenza vaccination has been proven to be effective in the prevention of serious complications or mortality of influenza. The effectiveness of anti-influenza drugs in the prevention of influenza complications requires further studies.<sup>15</sup>

### Vitamin C

Vitamin C has received a lot of attention since Pauling *et al* published a meta-analysis on four trials in 1971 claiming that its regular intake at a high dose (1-3 g) could half the incidence of the common cold.<sup>16</sup> However, the finding was not substantiated by subsequent randomised controlled trials and systematic reviews.<sup>16,17</sup> The systematic review on 30 trials by Douglas *et al* concluded that vitamin C at a dose of over 1 g might be able to reduce the duration of symptoms by an average of half a day, if it was taken at the onset of the illness but there was no evidence to show that it could reduce the incidence of URTI.<sup>16</sup>

### Zinc lozenges

Zinc can inhibit the growth of rhinoviruses *in vitro*. The first randomised controlled trial published by Eby *et al* showed that zinc lozenges every two-hours could shorten the average duration of a common cold by seven days but subsequent trials showed conflicting results.<sup>18</sup> A Cochrane systematic review on seven trials found some evidence suggesting that zinc lozenges could reduce the duration of cold symptoms by 1 to 3 days. A recent randomised double-blind placebo-controlled trial by Prasad *et al* also showed that zinc acetate lozenges could reduce the duration of cold symptoms by a mean of 3.6 days.<sup>19</sup> However, the use of zinc in clinical practice is limited by its frequent dosage requirement and high incidence (20%) of side effects including a metallic taste, nausea and oral mucosal irritation. Long-term use of zinc may interfere with copper metabolism. Further studies are required to determine the optimal preparation, dosage

and duration of treatment before zinc can be prescribed in routine clinical practice.

### Other agents

Mast cell stabilizers such as sodium cromoglycate have been shown to reduce the severity of URTI caused by rhinoviruses but their effectiveness has not been confirmed by clinical trials.<sup>17</sup>

Studies have failed to show any beneficial effect from Interferons for the cure of URTI's, although intranasal interferon alfa-2b has been shown to be effective for prophylaxis against rhinovirus infection if it is given before symptoms start. Interferons can cause nasal irritation, dryness and bleeding, which may cause more discomfort than the symptoms of URTI.<sup>17</sup>

Echinacea plant extract is a popular herbal treatment for URTI in Germany and other European countries. A systematic review on 14 trials by Melchart *et al* concluded that some Echinacea preparations might be better than placebo but most of the trials were of poor quality and publication bias could be present.<sup>20</sup>

### Symptomatic treatment for URTI

Symptomatic treatment cannot shorten the duration of the illness. At its best, it can decrease the severity of the symptoms so that the patient can feel more comfortable. Drugs should be prescribed only for symptoms that the patient finds distressing, otherwise, the side effects of treatment may produce more suffering than the URTI. More than one symptom may be caused by the same underlying pathology the treatment of which is more effective than giving a pill for every symptom.

### Systemic symptoms and sore throat

Paracetamol is proven to be effective in relieving the symptoms of fever, malaise and sore throat in both adults and children.<sup>21</sup> Aspirin and non-steroidal anti-inflammatory drugs are not much more effective than paracetamol but they are more prone to cause side effects. Aspirin is contraindicated in children under the age of 12 because of the risk of Reye's Syndrome.<sup>11,17</sup> There is no place for the use of prednisone or other glucocorticoids in the treatment of URTI because they have never been

shown to be effective in the prevention, cure or symptom relief of URTI.<sup>17</sup>

### Nasal symptoms

Antihistamines and alpha adrenergic agonists (nasal decongestants) are the most commonly used drugs for the relief of nasal symptoms associated with URTI.

Systemic non-selective antihistamines such as chlorpheniramine, doxylamine and clemastine have been shown to reduce the symptoms of sneezing and nasal discharge but the effects are modest.<sup>6,17,22</sup> Several clinical trials found that selective non-sedating antihistamines such as terfenadine were not effective, probably because they lack anticholinergic effects.<sup>17,23</sup> The evidence on the effectiveness of other antihistamines is inconclusive.<sup>17,22,23</sup> The data on children are limited, Smith *et al* found only four quality trials on children. One showed that antihistamine could reduce symptoms in pre-school children but another did not.<sup>22</sup> Two trials showed that combinations of analgesics, antihistamine and decongestant could reduce cough, sore throat and nasal symptoms in school children. Most trials did not find any adverse effects from antihistamines except one study showing excessive drowsiness in the treatment group.<sup>22</sup>

Alpha adrenergic agonists (nasal decongestants) are moderately effective in reducing nasal obstruction after a single dose in adults but there is no evidence to show that its benefit persists with subsequent doses.<sup>24</sup> Side effects including palpitation, dizziness, tremor, insomnia, tiredness and raised blood pressure have been reported in as many as 30% of the subjects treated with oral nasal decongestants.<sup>22</sup> They need to be used with care in patients with cardiovascular diseases or diabetes mellitus. Rebound congestion has been reported with prolonged use of topical decongestants.<sup>11,22</sup> There is also some concern for an association between cerebral haemorrhage and phenylpropanolamine.<sup>11</sup> Alpha adrenergic agonists should not be given to young children since there is no trial showing their effectiveness, and severe adverse effects have been reported in children, even after a single dose.<sup>22,24</sup>

### Cough

Cough in URTI is commonly secondary to postnasal drip or inflammation of the pharynx. Antihistamines that

reduce nasal discharge may already control the cough without the need of additional medications. Soothing drinks and analgesics can relieve the throat irritation from pharyngitis.

Cough mixtures contain one or a combination of substances ranging from simple syrup to potent drugs such as codeine. They are commonly prescribed for URTI but few of these substances have been proven to be effective in clinical trials.<sup>22,25</sup>

Opioid derivatives, including codeine, dextromethorphan and pholcodeine, and other cough suppressants, e.g. diphenhydramine, have only been shown to be effective in suppressing artificial or pathological chronic cough, are not superior to simple syrup in reducing cough associated with URTI.<sup>22,25</sup> There is little justification for giving an opioid cough suppressant for an URTI since they can lead to serious side effects and addiction.<sup>25</sup>

Inhaled or oral beta agonists have been found to be effective and superior to antibiotics in children and adults with prolonged (more than one week) cough associated with an URTI, especially in people with bronchial hypersensitivity.<sup>6,25</sup>

Most of the cough associated with URTI is dry, therefore, there is no rationale in prescribing mucolytics or expectorants. Clinical trials also failed to show any effectiveness from any of them in the relief of cough associated with URTI.<sup>22,25</sup>

### Patient expectation

Is it really true that patients in Hong Kong always expect a pill for every ill and want to have a large number of medications for even a minor URTI? Our earlier study showed that 23% of the people did not always expect drugs from a consultation.<sup>26</sup> Another local study found that although 91% expected medications from a consultation for an URTI, 57% of the subjects said that they would accept the doctor's advice for no medication if none was necessary.<sup>27</sup> Chan *et al* found that 78% of their subjects disagreed that more drugs were better<sup>27</sup> and 7% of the subjects in our study thought doctors gave them too many drugs.<sup>26</sup>

A more fundamental question is who is responsible for patients' expectation? Mainous *et al* showed that

### Key messages

1. Antibiotics are of no use for the common cold or sore throat with a negative throat swab.
2. Antibiotics may be beneficial for culture positive bacterial pharyngitis and rhinosinusitis.
3. Anti-influenza drugs can shorten the duration of influenza but there is inadequate evidence on the reduction of complication or mortality rates.
4. Non-steroidal anti-inflammatory drugs are not much more effective than paracetamol but have more side effects.
5. Non-selective antihistamines have modest effects on nasal symptoms.
6. Nasal decongestants may relieve nasal obstruction in adults but their effects for children are not proven.
7. People in Hong Kong do not always expect medications for their upper respiratory tract infections.
8. Rational prescribing requires the doctor to have the right attitude to his/her professional roles, up-to-date knowledge and effective communication skills.

creating previous antibiotic prescriptions increased the patients' expectation for antibiotics in subsequent consultations.<sup>28</sup> The patient may have learned to expect a lot of drugs from consultations because their doctors always prescribe, as evidenced by a prescription rate of 99.5% found in our earlier study.<sup>26</sup>

Prescribing drugs that are not proven to be effective to satisfy a patient's expectation for a fast cure or instantaneous relief is self-defeating because it will only lead to disappointment. Similarly, a shot-gun therapy of multiple drugs of doubtful indication is unlikely to hit the target but greatly increases the chance of side-effects.

### Rational prescribing

A doctor must have the correct attitude towards his/her professional roles of making an accurate diagnosis, treating for the benefit of the patient's health and doing no harm. A careful analysis of the nature and severity of the patient's illness can lead to rational prescribing of the least number of the most needed drugs. A doctor's management skills must include not only the prescribing

of drugs but also the ability to educate patients on the nature of URTI and to negotiate against unnecessary drug treatment.

Our health care system and culture may put pressure on doctors to prescribe but this is not an excuse for irrational prescribing. Irrational prescribing does not only harm the patient, it also damages the trust that patients and the society have in the medical profession. It may become a self-perpetuating vicious cycle if doctors do not put a stop to it. ■

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