REVIEW

Antibiotic prescribing for upper respiratory tract infections in the Asia-Pacific region: A brief review

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Abstract

This review highlights the high prevalence of antibiotic use for upper respiratory tract infections (URTIs) in a larger part of the Asia-Pacific region. Since URTIs are one of the common reasons for primary care consultations in this region, inappropriate use of antibiotic in both quantity and drug choice has greatly influenced the development of antibiotic resistance. Notwithstanding the paucity of Asia-Pacific data on the above issues, the available information suggests urgent actions needed to be taken to promote judicious antibiotic use at the point-of-care through a multi-pronged approach targeting the patients/consumers (or parents), healthcare providers and health care systems.

Introduction

Antibiotics loom large in the public imagination of the benefits of modern medical advances. Their introduction in the early twentieth century coincided with noticeable decline in mortality and improvement in quality of life of the general population. However, the improvement in social conditions and economic progress probably should receive more of that credit.[1] In the recent decades, the emergence of antibiotic resistance has been raising an alarm in the international stage and precipitating repeated calls for more judicious use of antibiotics.[2] Inappropriate antibiotic therapy in ambulatory care, especially for upper respiratory tract infections (URTIs), has been cited to have a major influence on the occurrence of antibiotic resistance.[2] This review therefore focuses on the problem of over-prescribing of antibiotics for URTIs and identifies the strategies that can be implemented to contain the problem. A comprehensive search for relevant original articles and systematic reviews has been done with a focus on the situation prevailing in the Asia-Pacific region. In this article, Asia-Pacific region has been taken in to the consideration including countries or political entities of East Asia (including South East Asia) and Oceania but excluding Russia and east coast of America).

In writing this review, answers of the following questions are sought:

1. What is the prevalence of group A beta-haemolytic *Streptococcus* isolation in children and adults presenting with URTIs?
2. What is the antibiotic prescribing rate for URTIs in primary care in the Asia-Pacific region?
3. What are the misconceptions regarding antibiotic use for URTIs?
4. What interventions have been done with the aim of reducing antibiotic prescribing rate in URTIs?

PubMed search was conducted using the combinations of relevant MESH terms (e.g., pharyngitis, respiratory tract infections, common colds, anti-bacterial agents, inappropriate prescribing, meta-analysis, etc.) supplemented by searching Google Scholar and checking reference section of the retrieved articles. Selected articles were primarily published between January 2000 and June 2014.

Definition

Anatomically speaking, upper respiratory tract refers to the part of the respiratory system that lies above the vocal cords. The phrase "upper respiratory tract infections (URTI)" has been defined inconsistently in the research literatures. The international classification of primary care (ICPC-2)[3] provided the following rubrics for six clinical conditions that some researchers would consider as URTI (see Box 1), whereas others limit the "URTI" only to presumed viral infection of the upper airways (rubric R74 in ICPC-2). In clinical practice, infections commonly affect two or

more contiguous areas of the upper airways; hence, words such as pharyngo-tonsillitis and rhinosinusitis are often used. In this review, the phrase "upper respiratory tract infections (URTIs)" was used, including ICPC-2 rubrics R72 to R77 but excluding R75 and H71.

Box 1: ICPC-2 rubrics for "URTI"

R72 : Strept throat (includes streptococcal pharyngitis)
R74 : Upper respiratory infections, acute (includes common cold, coryza and acute pharyngitis)
R75 : Sinusitis, acute/chronic
R76 : Tonsillitis, acute
R77 : Laryngitis/tracheitis
H71 : Otitis media, acute

Aetiology of URTIs

The aetiology of URTI is primarily viral in origin. Most of the viral infections are relatively benign, although, in recent years, serious epidemics have emerged where the initial presentations may be confused with the run-of-the-mill URTI, notably influenza A, severe acute respiratory syndrome (SARS), middle-east respiratory syndrome-corona virus (Mers-Cov).[4] It is generally believed that it is only the bacterial infection that deserves an antibiotic therapy is *Streptococcus pyogenes* (group A beta-haemolytic *Streptococcus* [GAS]).[5] In a meta-analysis of 29 prevalence studies, Shaikh et al. reported a *Streptococcus pyogenes* isolation rate of 37% among children with pharyngitis and 12% among healthy children.[6] However, none of the included studies were from the Asia-Pacific region. The isolation rates from the patients with URTIs in the Asia-Pacific regions vary from 0 to 28%. This wide variation is due to the numerous methodology issues, including selection criteria of patients (pharyngitis vs. others), patient's age, season and lack of consistency in the laboratory methods.[7-18]

Table 1. Prevalence of *Streptococcus pyogenes* isolation in children and adults with pharyngitis in Asia-Pacific studies published since 2000

Country	Author, Year	GAS prevalence (%)	Patients or prescriptions (n)	Setting
Australia	Danchin, 2004[7]	21	242 (all ages)	Primary care clinics
Australia	Bakare, 2010[8]	28	106 (all ages)	Primary care clinic
Fiji	Steer, 2009[9]	9	678 (children)	Four schools
Hong Kong	Wong, 2002[10]	3	1449 (all ages)	Hospital emergency department
Indonesia	Malino, 2013[11]	8	114 (children)	Hospital paediatric clinic and emergency room
Indonesia	Syahroel, 2008[12]	14	95 (children)	Hospital paediatric clinic
Japan	Hirakata, 2005[13]	7	930 (adults)	Primary care clinics and hospitals
Singapore	Hong, 2004[14]	0	594 (adults)	Public health centres
Thailand	Treebupachatsakul, 2006[15]	8	292 (adults)	Hospital outpatient clinic
Taiwan	Chi, 2003[16]	2	242 (children)	Hospital outpatient clinic
Taiwan	Lin, 2003[17]	21	1175 (children)	Hospital outpatient clinic
Taiwan	Shih, 2012[18]	4	342 (children)	Hospital outpatient clinic

Rationale for treating streptococcal pharyngo-tonsillitis

Untreated or inadequately treated streptococcal pharyngo-tonsillitis may result in suppurative and non-suppurative complications.[5] Rheumatic fever (a non-suppurative complication) may result from an autoimmune response to acute infection with Streptococcus pyogenes in the throat.[19] Rheumatic fever and its long-term cardiac sequelae (rheumatic heart disease) have been decreased markedly in the developed and developing countries.[20–22] However, they remain an important cause of morbidity and mortality in the aboriginal communities in Australia,[23] Pacific Islanders and Maori in New Zealand.[24,25] Underdiagnosis of this serious problem had been demonstrated in Fiji;[26] thus, the absence of data from many parts of the Asia-Pacific region may not mean that the problem has disappeared from the isolated deprived communities.

Clinical practice guidelines on streptococcal pharyngo-tonsillitis continue to recommend penicillin when the bacterial or streptococcal throat infection is strongly suspected on clinical grounds (see below). The antibiotic of choice is either a single dose of intramuscular procaine penicillin or a 10-day course of oral penicillin V.[27] This recommendation is based on the documented prevention of acute rheumatic fever with penicillin in military recruits way back in the 1950s.[28] Recent surveillance of Streptococcus pyogenes in the Asia-Pacific region revealed that the resistance of this bacterium to penicillin is non-existent but there is an increasing trend of resistance to erythromycin (China 95–98% and Hong Kong 28%).[29–31]

Diagnosis of streptococcal pharyngo-tonsillitis in primary care

Many diagnostic studies have been done with the aim of identifying clinical predictors of streptococcal pharyngo-tonsillitis. The most frequently used clinical prediction rule is based on a combination of five features (age <14 years, absence of cough, fever, cervical adenopathy, tonsillar swelling or exudates).[32] Patients without above features have very low chance of streptococcal infection and the diagnosis can be ruled out.[31] However, this clinical prediction rule is not specific for streptococcal infection in view of the marked overlaps in the symptoms/signs of viral and bacterial causes and the low prevalence of streptococcal infection in primary care.[33–34] Thus, even in patients with all the above five clinical predictors, the positive predictive value of Streptococcus pyogenes is still below 60%.[32]

The use of rapid strept screen has been advocated in high income countries, it has a relatively high specificity but a bit lower sensitivity (pooled specificity 96%, pooled sensitivity 85%, pooled likelihood ratio for positive test 22 and pooled likelihood ratio for negative test 0.15).[35] Thus, rapid strept screen demonstrated fairly good diagnostic performance but is somewhat better at ruling in streptococcal pharyngo-tonsillitis than ruling out this infection in the primary care. It is rarely used in the Asia-Pacific countries because of its cost.

Antibiotic prescribing rate and antibiotic choices

The antibiotic prescribing rates for URTI in the Asia-Pacific countries is highly variable (Table 2).[36–45] The reported rates are not directly comparable between countries in view of differences in the definition of URTI, period of study, sample size and study setting. Given that the prevalence of streptococcal infection among URTI patients is not more than approximately 20% (see Table 1); the available prescribing data suggest antibiotic over-prescribing in many countries, particularly in China, Thailand and Korea. The data also show that antibiotic choices may be inappropriate in some countries. For example, a study in Japan showed frequent use of broad-spectrum antibiotics that are more likely to promote antibiotic resistance. Penicillin V, the first choice recommendation in many guidelines, is rarely prescribed.

URTI, being a common reason for consultation in primary care in most countries, contributes a high proportion for antibiotic use in primary care. In Malaysia, it has been estimated that around 50% of all antibiotics used in primary care could be due to URTI (personal communication: Dr. Mohd Fozi Kamaruddin 1 August 2014).[42,46] In a systematic review using 243 studies, Bell et al. found that antibiotic consumption is associated with the development of antibiotic resistance.[47] In another systematic review conducted by Costelloe et al. individuals prescribed with an antibiotic in primary care for a respiratory infection were twice as likely to develop bacterial resistance to that antibiotic.[48] The effect was greatest in the month immediately after treatment but may persist up to 12 months.

Table 2. Antibiotic prescribing rates for URTI in the Asia-Pacific countries[a]

Country	Author, year	Setting	Patients or prescriptions (n)	Antibiotic prescribing rate (%)	Other remarks
Australia	Pan, 2006[36]	General practice clinics	2088	40% (adult) 24% (children)	Bettering evaluation and care of health (BEACH) data for the years 2002–2003
China	Jiang, 2012[37]	30 township health centres	3,059	85	25% of prescriptions contained two or more types of antibiotics
Hong Kong	Kung, 2014[38]	74 public clinics	895978	5	Computerised record for the year 2010
Japan	Higashi, 2009[39]	Outpatient clinics	2577	60	Outpatient visit claims in a health insurance plan. Types of antibiotics: Third-generation cephalosporin (46%), macrolide (27%) and quinolone (16%), penicillin (4%)
Korea	Park, 2005[40]	Outpatient clinics	16736	81	Viral illness (including URTI). Ambulatory visit claims in a national health insurance programme in 2000
Indonesia	Marjadi, 2009[41]	Outpatient clinics	6804	70 (public), 47 (private)	Extracted from PhD thesis
Malaysia	Fozi, 2013[42]	Outpatient clinics	22,328	34	Pre-intervention data in 2010. Antibiotic choices: macrolide 61%, penicillin 36% (penicillin V 0.4%)
New Zealand	Kljakovic, 2005[43]	246 GP clinics	335	61	10506 records from 246 GPs. Sore throat as a presentation
Taiwan	Hou, 2014[44]	Outpatient clinics	6915140	6	Ambulatory visit claims in a national health insurance programme
Thailand	Issarachaikul, 2013[45]	Outpatient clinics	339	81	Antibiotic choices: Penicillin, 71%, macrolide 21%

[a]The largest and latest study for each country has been preferentially cited.

Determinants of over-prescription of antibiotics

Systematic reviews of multiple studies revealed that there are multiple factors at the level of patients, healthcare providers and healthcare system that work in concerts to influence and maintain high antibiotic use. The factors have been described in detail in Table 3.

Table 3. Determinants of over-prescription of antibiotics with details

Categories	Factors
Patient factors[49–51]	Excessive patient expectation
	Lack of knowledge
	Misconception about antibiotics' effectiveness
Healthcare provider factors[52,53]	Diagnostic uncertainty
	Fear of complications or medico-legal problems
	Financial incentives of over-prescribing
	Lack of communication skills
	Physicians' complacency
	Undue weight given to non-predictors
Health system factors[54]	Cost constraints
	Lack of rapid laboratory tests
	Patient overload
	Pharmaceutical promotion

Interventions to reduce antibiotic prescribing

Various interventional studies have been done with the aim of reducing antibiotic prescriptions in URTI. Narrow scope interventions focusing the key steps of the point-of-care using diagnostic aids (e.g. C-reactive protein[55]) and fairly straightforward management strategy (delayed antibiotic prescribing[56]) do work but they are not practiced routinely in the Asia-Pacific region. Four systematic reviews[57–60] examining the effectiveness of patients/consumer education and provider education (see Table 4) have ben published. They generally employed the combinations of various active and passive strategies demonstrated to be effective by the Cochrane review group on Effective Practice and Organisation of Care, including medical audit, opinion leaders, academic detailing, and reminders. Only a few Asia-Pacific countries have tested some of these interventions; clearly, more studies need to be done in this region to determine their exact role.

In recent years, several Asia-Pacific countries have introduced national health financing schemes (e.g. Japan, Korea, Taiwan, Australia and New Zealand), and others are in various stages of planning the same (e.g. China, Indonesia and Malaysia). The systematic review by Faden et al.[61] identified more than 60 studies from low and medium income countries assessing the impact of health insurance system on inappropriate medicine utilisation. While health insurance system may improve the access to medicines, there is still a paucity of evidence showing its positive impact on appropriate medicine utilisation.

Radyowijati et al, in an extensive review of publications from the developing world, identified multiple stakeholders in the maintenance of the culture of prescribing inappropriate antibiotic.[54] They felt that professional education has limited effect and the sustained use of appropriate antibiotics in the community is achievable if there are multi-prong approaches by governments, health training institutions, professional societies, pharmaceutical companies, consumer organisations and international organisations.

Table 4. Systematic reviews of interventional studies aiming to reduce antibiotic use in primary care

Studies	Number of studies (*N*); study period	Countries studied	Intervention	Outcome
Huang, 2013[54]	N = 13; 1946–2013	Six countries from Europe and North America. None from Asia-Pacific region	Point-of-care C-reactive protein testing	Significantly reduced antibiotic prescribing at the index consultation for patients with RTIs
Spurling, 2013[55]	N = 10; 1966–2013	Four countries contributed all studies. New Zealand is represented	Delayed antibiotics	Reduced antibiotic use but is perceived as less satisfactory than immediate prescription by patients
Huttner, 2010[56]	N = 22; 1990–2007	16 countries, mostly from Europe and North America. Australia and New Zealand represented	Multi-faceted intervention (targeting both consumers and healthcare providers, using a variety of mass media and other interventions (guidelines, seminars, and academic detailing)	Costs of campaigns are high but probably contributed to more careful use of antibiotics in the outpatient settings
Vodicka, 2013[57]	N = 17; 1966–2012	Six high-income countries, mostly from Europe and North America. Australia represented	Multi-faceted intervention (combinations of patient education materials, group education, academic detailing, opinion leaders, prescribing feedback, computerised decision support system, reminders, websites	Interventions that combined parent education with clinician behaviour change decreased antibiotic prescribing rates by between 6–21%
Ivanovska, 2013[58]	N = 8; 1990–2009	Six high middle income countries. China and Malaysia are represented	Combinations of consumer and provider education	Greater impact on antibiotic prescribing was achieved by multifaceted interventions focusing on specific diseases
Andrews, 2012[59]	N = 23; 1966–2011	Three countries contributed all studies (Israel, UK and USA)	Verbal or written information given to parents or their children	In order to be most effective, interventions to influence parental consulting and antibiotic use should: Engage children, occur before an illness episode, employ delayed prescribing, and provide guidance on specific symptoms

Conclusion

The above review has documented the antibiotic overuse in URTI, which is a major problem in much of the Asia-Pacific region. Since URTI forms a large proportion of the reason for primary care consultations in this region, inappropriate use of antibiotic in both quantity and drug choice exert major selective pressure on the occurrence of antibiotic resistance. Although, there is a paucity of national level data on the above issues, the available information suggests an urgent need to take actions to promote judicious antibiotic use at the point-of-care through a multi-prong approach targeting the patient/consumer, healthcare providers and health care system.

Conflict of interest

None.

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