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MAHIDOL UNIVERSITY
Wisdom of the Land
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Common Infectious Diseases in Pediatrics

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Respiratory Tract Infections

Upper RTIs

- Rhinitis
- Influenza
- Pharyngitis / tonsillitis
- Rhinosinusitis

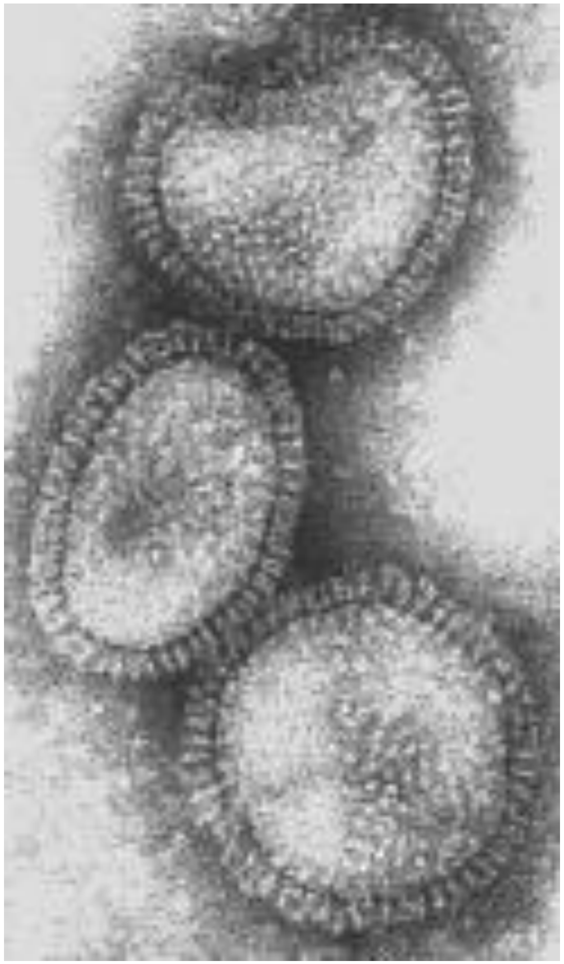
Lower RTIs

- Bronchitis
- Bronchiolitis
- Pneumonia

Respiratory Virus Infections

Syndrome	Commonly Associated Viruses	Less Commonly Associated Viruses
Coryza	Rhinoviruses, coronaviruses	Influenza viruses, parainfluenza viruses, enteroviruses, adenoviruses
Influenza	Influenza viruses	Parainfluenza viruses, adenoviruses
Croup	Parainfluenza viruses	Influenza viruses, RSV, adenoviruses
Bronchiolitis	RSV, rhinoviruses	Influenza viruses, parainfluenza viruses, adenoviruses, hMPV

Influenza Virus



- 3 types: A, B, and C
- Type A undergoes antigenic shift and drift
- Influenza A subtypes : HA and NA
- Type B undergoes antigenic drift only and type C is relatively stable

Influenza A Virus

- Antigenic shifts of the HA results in pandemics
- Antigenic drifts in the HA and NA result in epidemics

Influenza: Laboratory Diagnosis

- Rapid diagnosis: Detection of antigen from nasopharyngeal aspirates and throat washings
  - Sensitivity 50-70%, specificity >90%
- Virus Isolation – Culture or PCR from nasopharyngeal aspirates and throat swabs

Treatment Recommendation

- Treatment with oseltamivir, zanamivir, or baloxavir is recommended for:
  - Persons with suspected or confirmed influenza with severe illness (e.g. hospitalized patients)
  - Persons with suspected or confirmed influenza who have risk factors for severe illness

Risk Factors For Severe Influenza Illness

- Aged <2 yrs, ≥65 yrs
- Person with medical conditions, immunosuppression, conditions that compromise respiratory function
- Obesity
- Pregnant women and <2 weeks postpartum
- Receiving long term aspirin therapy

Types of seasonal influenza vaccine

Type of vaccines
Inactivated, Live-attenuated, Cell culture

Trivalent (TIV)

A-H1N1

A-H3N2

B-Yamagata OR B-Victoria

Tetravalent (QIV)

A/H1N1

A/H3N2

B-Yamagata AND B-Victoria

WHO 2019 (Southern hemisphere)

A/Michigan/45/2015 (H1N1)pdm09-like virus
A/Switzerland/8060/2017 (H3N2)-like virus
B/Colorado/06/2017-like virus (B/Victoria/2/87 lineage)

B/Phuket/3073/2013-like virus (B/Yamagata/16/88 lineage)

WHO 2019/20 (Northern hemisphere)

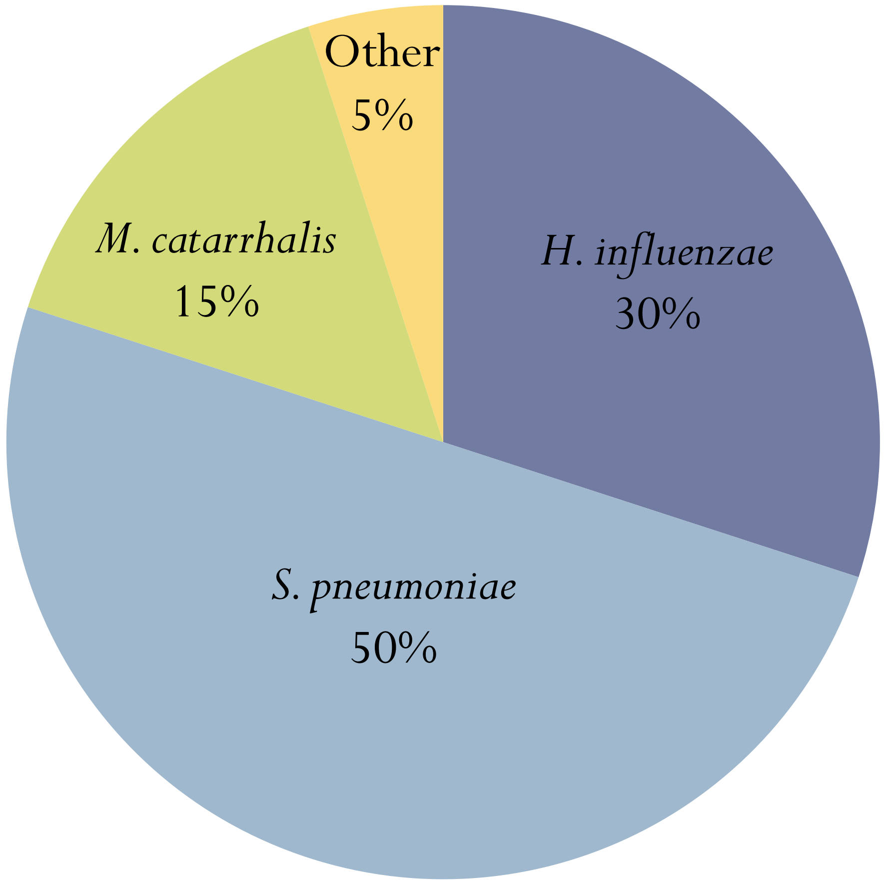
A/Brisbane/02/2018 (H1N1)pdm09-like virus
A/Kansas/14/2017 (H3N2)-like virus
B/Colorado/06/2017-like virus (B/Victoria/2/87 lineage)

B/Phuket/3073/2013-like virus (B/Yamagata/16/88 lineage)

http://www.who.int/influenza/vaccines/virus/recommendations/ Last

Acute Otitis Media

Acute Otitis Media: Bacterial Etiology



Barnett ED, et al. *Pediatr Clin North Am* 1995;42:509–517.
Jacobs MR. *Pediatr Infect Dis J* 1996;15:940–943.

Intakorn et al. BMC Pediatrics 2014, 14:157
http://www.biomedcentral.com/1471-2431/14/157

BMC Pediatrics

RESEARCH ARTICLE Open Access

Haemophilus influenzae type b as an important cause of culture-positive acute otitis media in young children in Thailand: a tympanocentesis-based, multi-center, cross-sectional study

Pavinee Intakorn[1*], Nuntigar Sonsuwan[2], Suwiwan Noknu[3], Greetha Moungthong[4], Jean-Yves Pirçon[5], Yanfang Liu[6,7], Melissa K Van Dyke[5,8] and William P Hausdorff[5]

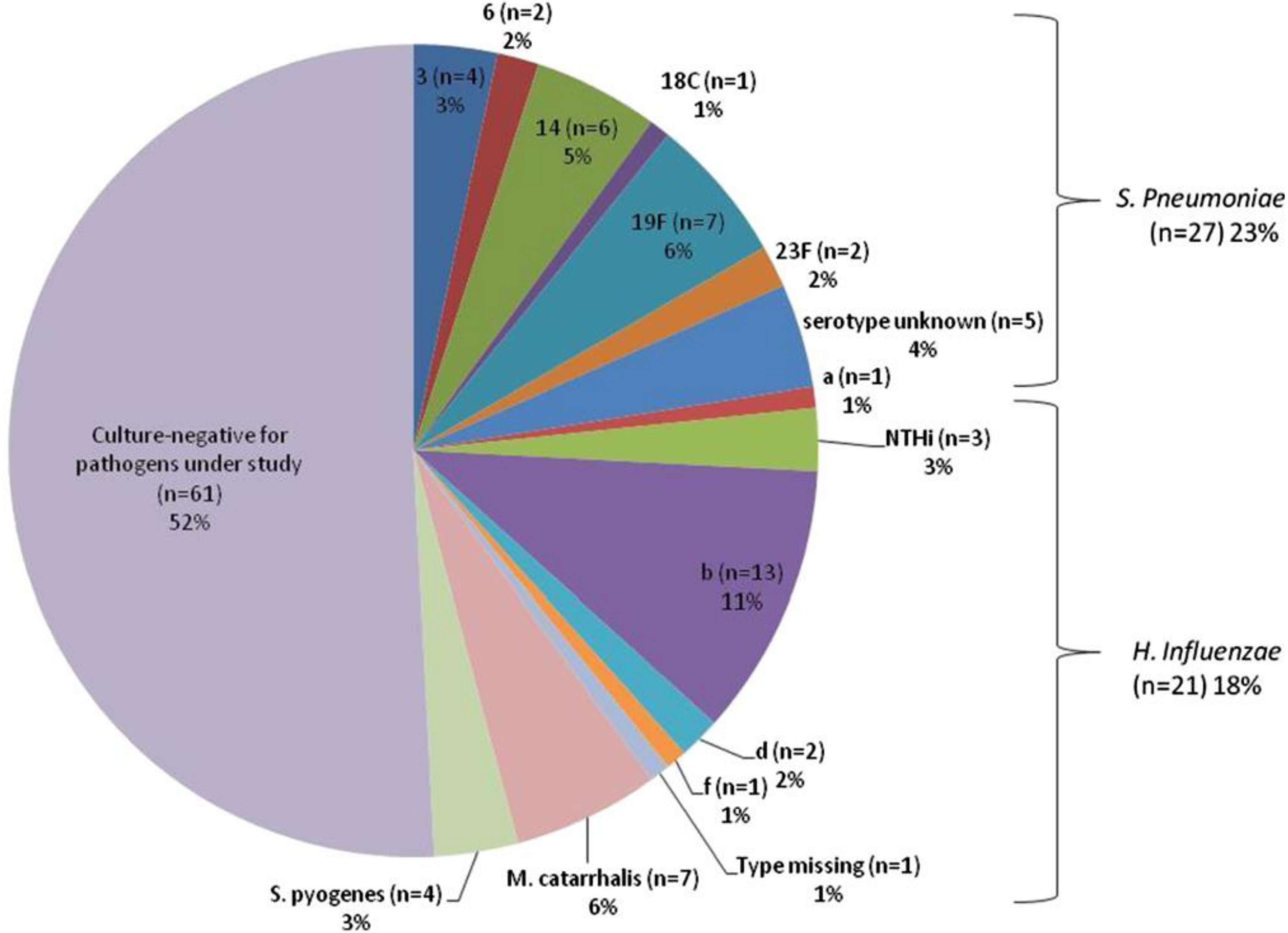


Figure 2 Culture results and pathogens under study identified from middle ear fluid samples (N = 118). Culture results from middle ear fluid samples including serotype distribution for *S. pneumoniae* (*Spn*, n = 27), and *H. influenzae* (*H. inf*, n = 21). There were two co-infected samples due to one co-infection of *S. pneumoniae* 23F and *H. influenzae* serotype a, and one co-infection of Hib and *M. catarrhalis*.

AOM spontaneous resolution rate varies by pathogen

Organism	Spontaneous bacteriologic clearance rate
S. pneumoniae	19%
H. influenzae	48%
M. catarrhalis	75%

Howie VM. Clin Infect Dis 1992;14:S209-10; Klein JO. PIDJ 1993;12:973-5

Risk Factors for Resistant S. *pneumoniae* Infection

- Age (≤2 years)
- Attendance at day-care centers
- Siblings of children attending day-care centers
- Not vaccinated with pneumococcal conjugate vaccine (PCV)
- Prior AOM within the past six months
- Receipt of antibiotics within the last three months

Working Group of the Infectious Diseases Society of Southern Africa. Updated guideline for the management of upper respiratory tract infections in South Africa: 2008. South Afr J Epidemiol Infect 2008;23(4):01-09

SOAR S/SE Asia (2012-14): main CA-RTI isolates

SOAR Study 2012-2014, Thailand

S. pneumoniae

Antimicrobial (N)[a]	CLSI (%S)	EUCAST (%S)	PK/PD (%S)
AMC[b,c] (N=208)	**97.1**	**NA**	**97.1(99)**
Penicillin (IV) (N=208)	98.1	84.1-98.1	NA
Penicillin oral (N=208)	49.0	49.0	NA
Cefuroxime[e] (N=208)	77.9	59.1	77.9
Levofloxacin (N=208)	98.1	98.1	98.1
Azithromycin[d] (N=208)	53.4	NA	NA
Clarithromycin[d] (N=208)	52.4	NA	NA
Erythromycin[f] (N=208)	51.9	51.9	NA

>90% Susceptible
90% to 75% Susceptible
<75% Susceptible

AMC=Amoxicillin/clavulanate

Torumkuney D, et al. J Antimicrob Chemother 2016;71(Suppl 1):i3–i19

SOAR S/SE Asia (2012-14): main CA-RTI isolates

SOAR Study 2012-2014, Thailand

H. influenzae

Antimicrobial (N)	CLSI (%S)	EUCAST (%S)	PK/PD (%S)
Amp [c]All (N=263)	51.7	51.7	NA
Amp BL+ (N=96)	1.0	1.0	NA
Amp BL – (N=167)	80.8	80.8	NA
AMC[a,b] All (N=263)	**97.7 (93.5)[f]**	**90.5 (81.4)[f]**	**90.5 (97.7)**
AMC BL + (N=96)	96.9	85.4	85.4 (96.9)
AMC BL – (N=167)	98.2	93.4	93.4 (98.2)
Cefu [e,b] All (N=263)	96.2 (92.4)[f]	7.2	79.5
Cefu BL + (N=96)	97.9	2.1	80.2
Cefu BL - (N=167)	95.2	10.1	79.0
Azithromycin[d] ALL (N=263)	99.6	NA	NA
Clarithromycin [d] ALL (N=263)	79.5	NA	NA
Levofloxacin ALL (N=263)	99.6	99.2	99.6

>90% Susceptible

90% to 75% Susceptible

<75% Susceptible

AMC=Amoxicillin/clavulanate

Torumkuney D, et al. J Antimicrob Chemother 2016;71(Suppl 1):i3–i19

SOAR Study 2012-2014, 4 centers in Thailand

Moraxella catarrhalis, 100% beta-lactamase production

Antimicrobial	N	MIC (mg/L)				Susceptibility						
						CLSI			PK/PD	EUCAST		
		50%	90%	MIN	MAX	%S	%I	%R	%S	%S	%I	%R
AMC	49	0.25	0.5	0.03	0.5	100	0	0	100 (100)	100	0	0
Azithromycin	49	0.25	1	≤0.015	>256	NA	NA	NA	NA	NA	NA	NA
Cefuroxime	49	1	2	0.06	4	100	0	0	63.3	2	98	0
Clarithromycin	49	0.25	1	0.03	>256	NA	NA	NA	NA	NA	NA	NA
Levofloxacin	49	0.06	0.12	0.03	>32	98	0	2	98	98	0	2

TABLE 8. MIC and susceptibility results for M. Catarrhalis Thailand. Torumkuney et al. J Antimicrob Chemother 2016; 71 Suppl 1: i3–i19

Management of AOM

TABLE 4 Recommendations for Initial Management for Uncomplicated AOM[a]

Age	Otorrhea With AOM[a]	Unilateral or Bilateral AOM[a] With Severe Symptoms[b]	Bilateral AOM[a] Without Otorrhea	Unilateral AOM[a] Without Otorrhea
6 mo to 2 y	Antibiotic therapy	Antibiotic therapy	Antibiotic therapy	Antibiotic therapy or additional observation
≥2 y	Antibiotic therapy	Antibiotic therapy	Antibiotic therapy or additional observation	Antibiotic therapy or additional observation[c]

[a] Applies only to children with well-documented AOM with high certainty of diagnosis (see Diagnosis section).
[b] A toxic-appearing child, persistent otalgia more than 48 h, temperature ≥39°C (102.2°F) in the past 48 h, or if there is uncertain access to follow-up after the visit.
[c] This plan of initial management provides an opportunity for shared decision-making with the child's family for those categories appropriate for additional observation. If observation is offered, a mechanism must be in place to ensure follow-up and begin antibiotics if the child worsens or fails to improve within 48 to 72 h of AOM onset.

Lieberthal AS, et al. *Pediatrics.* 2013;131:e964–e999.

Management of AOM

Antibiotic Therapy

TABLE 5 Recommended Antibiotics for (Initial or Delayed) Treatment and for Patients Who Have Failed Initial Antibiotic Treatment

Initial Immediate or Delayed Antibiotic Treatment		Antibiotic Treatment After 48–72 h of Failure of Initial Antibiotic Treatment	
Recommended First-line Treatment	Alternative Treatment (if Penicillin Allergy)	Recommended First-line Treatment	Alternative Treatment
Amoxicillin (80–90 mg/ kg per day in 2 divided doses)	Cefdinir (14 mg/kg per day in 1 or 2 doses)	Amoxicillin-clavulanate[a] (90 mg/kg per day of amoxicillin, with 6.4 mg/kg per day of clavulanate in 2 divided doses)	Ceftriaxone, 3 d Clindamycin (30–40 mg/kg per day in 3 divided doses), with or without third-generation cephalosporin
or	Cefuroxime (30 mg/kg per day in 2 divided doses)	or	Failure of second antibiotic
Amoxicillin-clavulanate[a] (90 mg/kg per day of amoxicillin, with 6.4 mg/kg per day of clavulanate [amoxicillin to clavulanate ratio, 14:1] in 2 divided doses)	Cefpodoxime (10 mg/kg per day in 2 divided doses)	Ceftriaxone (50 mg IM or IV for 3 d)	Clindamycin (30–40 mg/kg per day in 3 divided doses) plus third-generation cephalosporin Tympanocentesis[b] Consult specialist[b]
	Ceftriaxone (50 mg IM or IV per day for 1 or 3 d)		

IM, intramuscular; IV, intravenous.

[a] May be considered in patients who have received amoxicillin in the previous 30 d or who have the otitis-conjunctivitis syndrome.

[b] Perform tympanocentesis/drainage if skilled in the procedure, or seek a consultation from an otolaryngologist for tympanocentesis/drainage. If the tympanocentesis reveals multidrug-resistant bacteria, seek an infectious disease specialist consultation.

[c] Cefdinir, cefuroxime, cefpodoxime, and ceftriaxone are highly unlikely to be associated with cross-reactivity with penicillin allergy on the basis of their distinct chemical structures. See text for more information.

Lieberthal AS, et al. *Pediatrics.* 2013;131:e964–e999.

Management of AOM

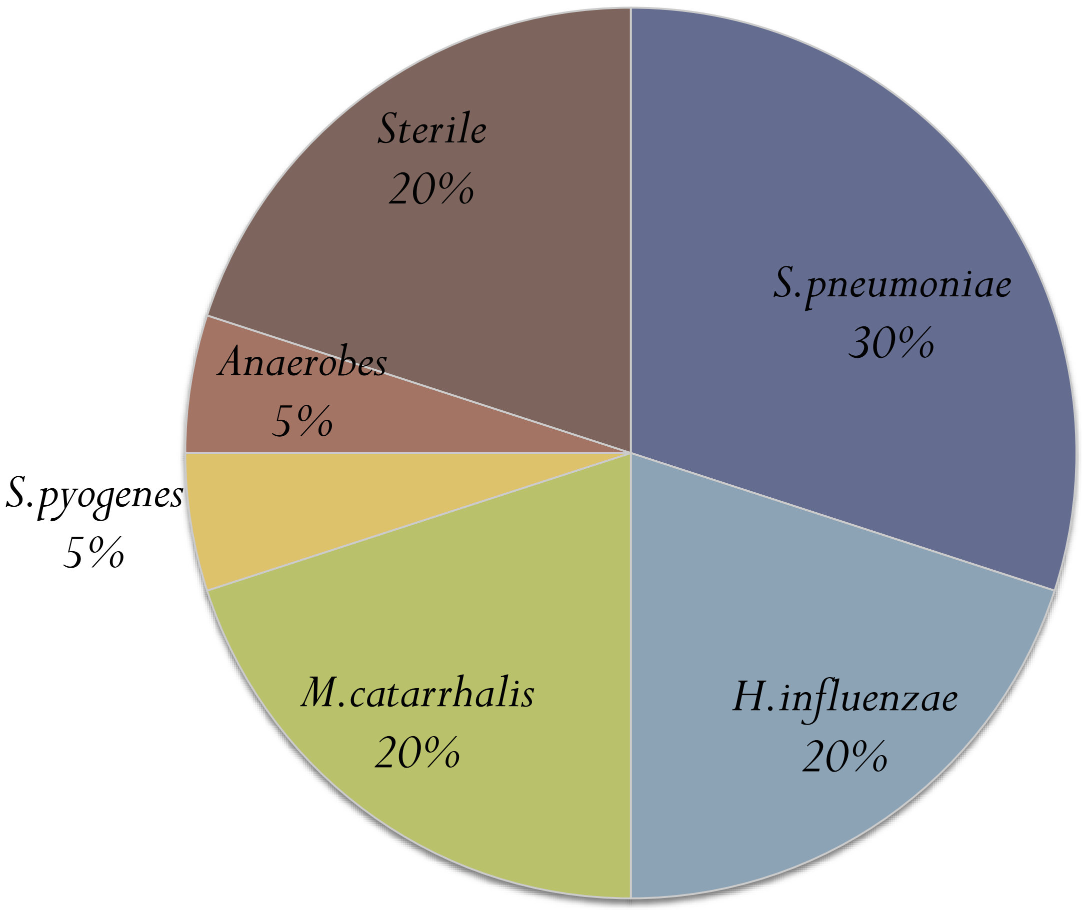
Duration of Therapy

- In children ≤ 2 years and children with severe symptoms,
  - a standard 10-day course is recommended.
- In children 2 to 5 years with mild or moderate AOM,
  - A 7-day course of oral antibiotic appears to be equally effective.
- In children ≥ 6 years with mild to moderate symptoms
  - 5- to 7-day course is adequate treatment.

Lieberthal AS, et al. *Pediatrics.* 2013;131:e964–e999.

Acute Bacterial Rhinosinusitis

Microbiology of Acute Bacterial Rhinosinusitis (Children)



Otolaryngology – Head and Neck Surgery; Jan 2004.

Criteria for the Diagnosis of Sinusitis

- Presence of at least 2 major or 1 major and ≥2 minor symptoms

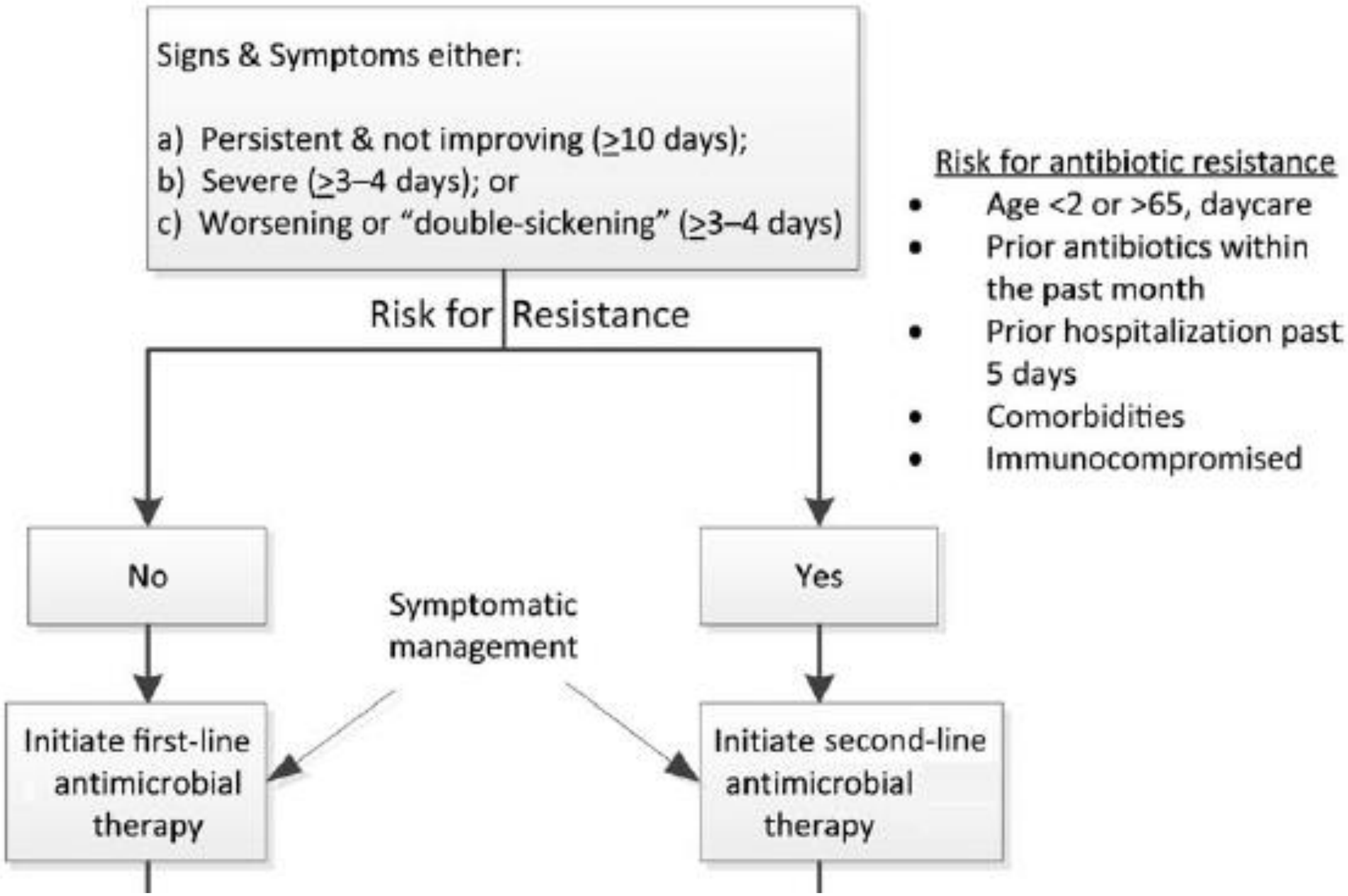
Table 2. Conventional Criteria for the Diagnosis of Sinusitis Based on the Presence of at Least 2 Major or 1 Major and ≥2 Minor Symptoms

Major Symptoms	Minor Symptoms
• Purulent anterior nasal discharge	• Headache
• Purulent or discolored posterior nasal discharge	• Ear pain, pressure, or fullness
• Nasal congestion or obstruction	• Halitosis
• Facial congestion or fullness	• Dental pain
• Facial pain or pressure	• Cough
• Hyposmia or anosmia	• Fever (for subacute or chronic sinusitis)
• Fever (for acute sinusitis only)	• Fatigue

Modified from Meltzer et al [7].

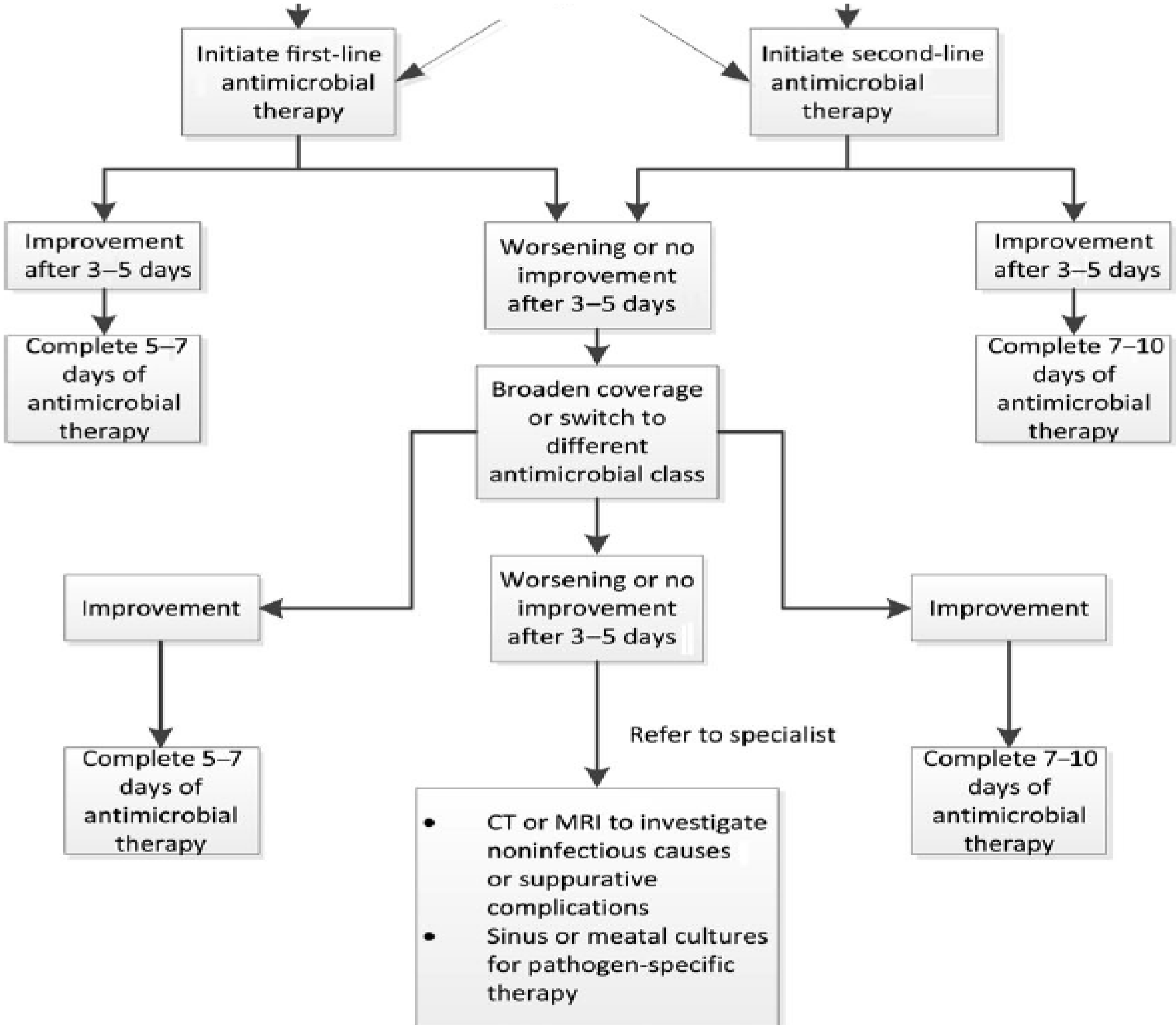
Chow AW, et al. *Clin Infect Dis*. 2012; 54:e72-e112.

Algorithm for the Management of Acute Bacterial Rhinosinusitis: IDSA 2012



Chow AW, et al. *Clin Infect Dis*. 2012; 54:e72-e112.

Algorithm for the Management of Acute Bacterial Rhinosinusitis: IDSA 2012



Chow AW, et al. *Clin Infect Dis*. 2012; 54:e72-e112.

Recommendations for Initial Use of Antibiotics for Acute Bacterial Sinusitis

TABLE 2 Recommendations for Initial Use of Antibiotics for Acute Bacterial Sinusitis

Clinical Presentation	Severe Acute Bacterial Sinusitis[a]	Worsening Acute Bacterial Sinusitis[b]	Persistent Acute Bacterial Sinusitis[c]
Uncomplicated acute bacterial sinusitis without coexisting illness	Antibiotic therapy	Antibiotic therapy	Antibiotic therapy or additional observation for 3 days[d]
Acute bacterial sinusitis with orbital or intracranial complications	Antibiotic therapy	Antibiotic therapy	Antibiotic therapy
Acute bacterial sinusitis with coexisting acute otitis media, pneumonia, adenitis, or streptococcal pharyngitis	Antibiotic therapy	Antibiotic therapy	Antibiotic therapy

[a] Defined as temperature ≥39°C and purulent (thick, colored, and opaque) nasal discharge present concurrently for at least 3 consecutive days.

[b] Defined as nasal discharge or daytime cough with sudden worsening of symptoms (manifested by new-onset fever ≥38°C/100.4°F or substantial increase in nasal discharge or cough) after having experienced transient improvement of symptoms.

[c] Defined as nasal discharge (of any quality), daytime cough (which may be worse at night), or both, persisting for >10 days without improvement.

[d] Opportunity for shared decision-making with the child's family; if observation is offered, a mechanism must be in place to ensure follow-up and begin antibiotics if the child worsens at any time or fails to improve within 3 days of observation.

Wald ER, et al. *Pediatrics*. 2013;132:e262-80.

IDSA Clinical Practice Guideline for Acute Bacterial Rhinosinusitis

Prevalence (Mean Percentage of Positive Specimens) of Various Respiratory Pathogens From Sinus Aspirates in Patients With Acute Bacterial Rhinosinusitis

	Publications Before 2000		Publications in 2010	
Microbial Agent	Adults[a] (%)	Children[b] (%)	Adults[c] (%)	Children[d] (%)
Streptococcus pneumoniae	30–43	44	38	21–33
Haemophilus influenzae	31–35	30	36	31–32
Moraxella catarrhalis	2–10	30	16	8–11
Streptococcus pyogenes	2–7	2	4	…
Staphylococcus aureus	2–3	…	13	1
Gram-negative bacilli (includes *Enterobacteriaceae* spp)	0–24	2	…	…
Anaerobes *(Bacteroides, Fusobacterium, Peptostreptococcus)*[e]	0–12	2	…	…
Respiratory viruses	3–15	…	…	…
No growth	40–50	30	36	29

Chow AW, et al. *Clin Infect Dis*. 2012 Apr;54:e72-e112.

IDSA Clinical Practice Guideline for Acute Bacterial Rhinosinusitis

- Antimicrobial Regimens for Acute Bacterial Rhinosinusitis in Children

Indication	First-line (Daily Dose)	Second-line (Daily Dose)
Initial empirical therapy	• Amoxicillin-clavulanate (45 mg/kg/day PO bid)	• Amoxicillin-clavulanate (90 mg/kg/day PO bid)
β-lactam allergy		
Type I hypersensitivity		• Levofloxacin (10–20 mg/kg/day PO every 12–24 h)
Non–type I hypersensitivity		• Clindamycin[a] (30–40 mg/kg/day PO tid) plus cefixime (8 mg/kg/day PO bid) or cefpodoxime (10 mg/kg/day PO bid)
Risk for antibiotic resistance or failed initial therapy		• Amoxicillin-clavulanate (90 mg/kg/day PO bid)
		• Clindamycin[a] (30–40 mg/kg/day PO tid) plus cefixime (8 mg/kg/day PO bid) or cefpodoxime (10 mg/kg/day PO bid)
		• Levofloxacin (10–20 mg/kg/day PO every 12–24 h)
Severe infection requiring hospitalization		• Ampicillin/sulbactam (200–400 mg/kg/day IV every 6 h)
		• Ceftriaxone (50 mg/kg/day IV every 12 h)
		• Cefotaxime (100–200 mg/kg/day IV every 6 h)
		• Levofloxacin (10–20 mg/kg/day IV every 12–24 h)

Abbreviations: bid, twice daily; IV, intravenously; PO, orally; qd, daily; tid, 3 times a day.

[a] Resistance to clindamycin (~31%) is found frequently among *Streptococcus pneumoniae* serotype 19A isolates in different regions of the United States [94].

Chow AW, et al. *Clin Infect Dis*. 2012 Apr;54(8):e72-e112.

Pneumonia

Causes – 1 to 3 months

- Viruses: RSV, parainfluenza virus
- *Chlamydia trachomatis* (2-8 weeks)
  - Afebrile, tachypnea, CXR with interstitial infiltrates, eosinophilia
- *B. pertussis*
  - Tracheobronchitis with severe paroxysmal cough, no fever
  - Pneumonia usually related to aspiration

Causes – 3 months to 4 years

- Viruses: RSV, parainfluenza, influenza, adenovirus, hMPV, rhinovirus, coronaviruses
- *S. pneumoniae*: Related suppurative complications
- *H. influenzae* type B
- *S. aureus*
- *M. pneumoniae*, *C. pneumoniae*

Causes – 5 years through adolescence

- *M. pneumoniae*
- *C. pneumoniae*
- *S. pneumoniae*
- Viruses: Smaller percentage

IDSA GUIDELINES

The Management of Community-Acquired Pneumonia in Infants and Children Older Than 3 Months of Age: Clinical Practice Guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America

John S. Bradley,[1,a] Carrie L. Byington,[2,a] Samir S. Shah,[3,a] Brian Alverson,[4] Edward R. Carter,[5] Christopher Harrison,[6] Sheldon L. Kaplan,[7] Sharon E. Mace,[8] George H. McCracken Jr,[9] Matthew R. Moore,[10] Shawn D. St Peter,[11] Jana A. Stockwell,[12] and Jack T. Swanson[13]

Bradley JS, et al. *Clin Infect Dis*. 2011;53:e25-76.

Table 7. Empiric Therapy for Pediatric Community-Acquired Pneumonia (CAP)

Site of care	Empiric therapy: Presumed bacterial pneumonia	Empiric therapy: Presumed atypical pneumonia	Empiric therapy: Presumed influenza pneumonia[a]
Outpatient			
<5 years old (preschool)	Amoxicillin, oral (90 mg/kg/day in 2 doses[b]) Alternative: oral amoxicillin clavulanate (amoxicillin component, 90 mg/kg/day in 2 doses[b])	Azithromycin oral (10 mg/kg on day 1, followed by 5 mg/kg/day once daily on days 2–5); Alternatives: oral clarithromycin (15 mg/kg/day in 2 doses for 7-14 days) or oral erythromycin (40 mg/kg/day in 4 doses)	Oseltamivir
≥5 years old	Oral amoxicillin (90 mg/kg/day in 2 doses[b] to a maximum of 4 g/day[c]); for children with presumed bacterial CAP who do not have clinical, laboratory, or radiographic evidence that distinguishes bacterial CAP from atypical CAP, a macrolide can be added to a β-lactam antibiotic for empiric therapy; alternative: oral amoxicillin clavulanate (amoxicillin component, 90 mg/kg/day in 2 doses[b] to a maximum dose of 4000 mg/day, eg, one 2000-mg tablet twice daily[b])	Oral azithromycin (10 mg/kg on day 1, followed by 5 mg/kg/day once daily on days 2–5 to a maximum of 500 mg on day 1, followed by 250 mg on days 2–5); alternatives: oral clarithromycin (15 mg/kg/day in 2 doses to a maximum of 1 g/day); erythromycin, doxycycline for children >7 years old	Oseltamivir or zanamivir (for children 7 years and older); alternatives: peramivir, oseltamivir and zanamivir (all intravenous) are under clinical investigation in children; intravenous zanamivir available for compassionate use

Bradley JS, et al. *Clin Infect Dis*. 2011;53:e25-76.

Table 7. Empiric Therapy for Pediatric Community-Acquired Pneumonia (CAP)

	Empiric therapy		
Site of care	Presumed bacterial pneumonia	Presumed atypical pneumonia	Presumed influenza pneumonia[a]
Inpatient (all ages)[d]			
Fully immunized with conjugate vaccines for *Haemophilus influenzae* type b and *Streptococcus pneumoniae*; local penicillin resistance in invasive strains of pneumococcus is minimal	Ampicillin or penicillin G; alternatives: ceftriaxone or cefotaxime; addition of vancomycin or clindamycin for suspected CA-MRSA	Azithromycin (in addition to β-lactam, if diagnosis of atypical pneumonia is in doubt); alternatives: clarithromycin or erythromycin; doxycycline for children >7 years old; levofloxacin for children who have reached growth maturity, or who cannot tolerate macrolides	Oseltamivir or zanamivir (for children ≥7 years old; alternatives: peramivir, oseltamivir and zanamivir (all intravenous) are under clinical investigation in children; intravenous zanamivir available for compassionate use
Not fully immunized for *H, influenzae* type b and *S. pneumoniae*; local penicillin resistance in invasive strains of pneumococcus is significant	Ceftriaxone or cefotaxime; addition of vancomycin or clindamycin for suspected CA-MRSA; alternative: levofloxacin; addition of vancomycin or clindamycin for suspected CA-MRSA	Azithromycin (in addition to β-lactam, if diagnosis in doubt); alternatives: clarithromycin or erythromycin; doxycycline for children >7 years old; levofloxacin for children who have reached growth maturity or who cannot tolerate macrolides	As above

Bradley JS, et al. *Clin Infect Dis*. 2011;53:e25-76.

Recommendations: Duration of Antimicrobial Therapy

- Treatment courses of 10 days have been best studied, although shorter courses may be just as effective, particularly for more mild disease managed on an outpatient basis. (strong recommendation; moderate-quality evidence)
- Infections caused by certain pathogens, notably CA-MRSA, may require longer treatment than those caused by *S. pneumoniae*. (strong recommendation; moderate-quality evidence)

Bradley JS, et al. *Clin Infect Dis*. 2011;53:e25-76.

Pertussis in Thai Children

- QSNIC, Prospective study
- Subjects:

  - Children with cough > 7 days (Paroxysm, whooping cough, vomiting)

  - 96 patients: NB-15.4 yrs, median 7.7 mo.

  - DTP = 3 doses 49%, <3 doses 46.9%

  - PCR for pertussis: Positive 19%

Santarattivong P, PIDST Meeting, May 2013

Bordetella pertussis

- 3 stages
  - Catarrhal stage: similar to common cold
  - Paroxysmal stage: whooping cough, post-tussis emesis, apnea, cyanosis, paroxysmal events
  - Convalescent stage: symptoms wane gradually
- Fever is absent or minimal
- Conjunctival hemorrhage, petechiae on the upper body

Complications of Pertussis

Infants < 12 months of age

- 1 in 5 Pneumonia
- 1 in 100 Convulsions
- 1 in 2 Apnea
- 1 in 300 Encephalopathy
- 1 in 100 Die

Adolescents and Adults

- Weight loss (33%)
- Urinary incontinence (28%)
- Syncope (6%)
- Rib fractures (4%)

Hospitalization is most common in infants <6 months of age.

Cortese MM, Bisgard KM. Pertussis. In: Wallace RB, Kohatsu N, Kast JM, ed. Maxcy-Rosenau-Last Public Health & Preventive Medicine, Fifteenth Edition. The McGraw-Hill Companies, Inc.; 2008:111-14.

Bordetella pertussis

- CBC: leukocytosis, lymphocytosis and thrombocytosis
- CXR: perihilar infiltration or interstitial edema
- Diagnosis: culture remains gold-standard, PCR
- Treatment: erythromycin, clarithromycin, azithromycin, TMP/SMX (alternative drugs)

Tuberculosis

Risk of Disease Following Primary Infection

	Risk of disease following primary infection			Comments
	Disseminated tuberculosis/ tuberculosis meningitis	Pulmonary tuberculosis	No disease	
<1 years	10–20%	30–40%	50%	High rates of morbidity and mortality
1–2 years	2–5%	10–20%	75–80%	High rates of morbidity and mortality
2–5 years	0·5%	5%	95%	..
5–10 years	<0·5%	2%	98%	"Safe school years"
>10 years	<0·5%	10–20%	80–90%	Effusions or adult-type pulmonary disease

Adapted from reference 30.

Table 1: **Risk of pulmonary and extrapulmonary disease in children following infection with *Mycobacterium tuberculosis***

Newton SM, et al. *Lancet Infect Dis* 2008;8:498-510.

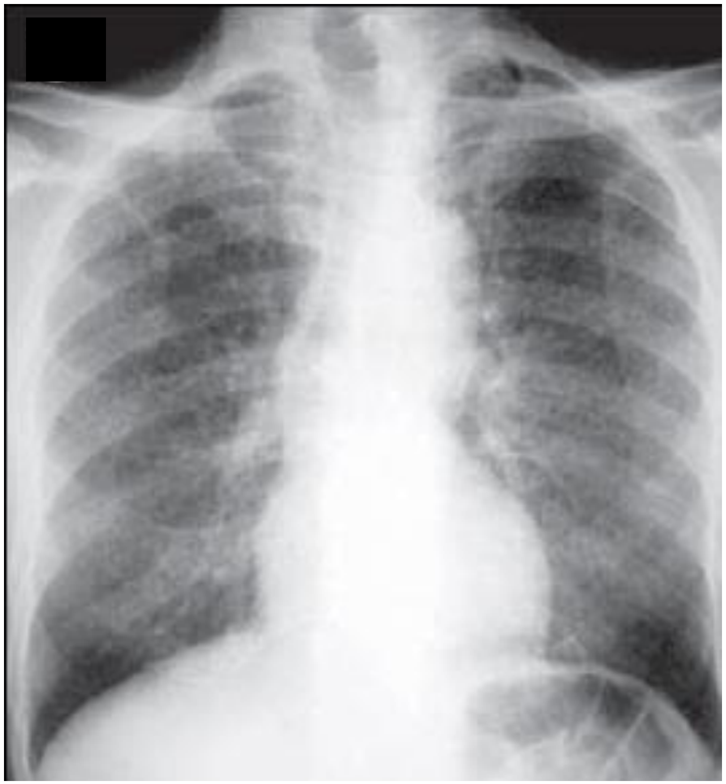
Clinical Manifestations

- The most common site of infection is the lung (up to 80%)
- Extrapulmonary manifestation
  - Lymphadenopathy 67%
  - Meningitis 13%
  - Pleural TB 6%
  - Miliary TB 5%
  - Skeletal TB 4%

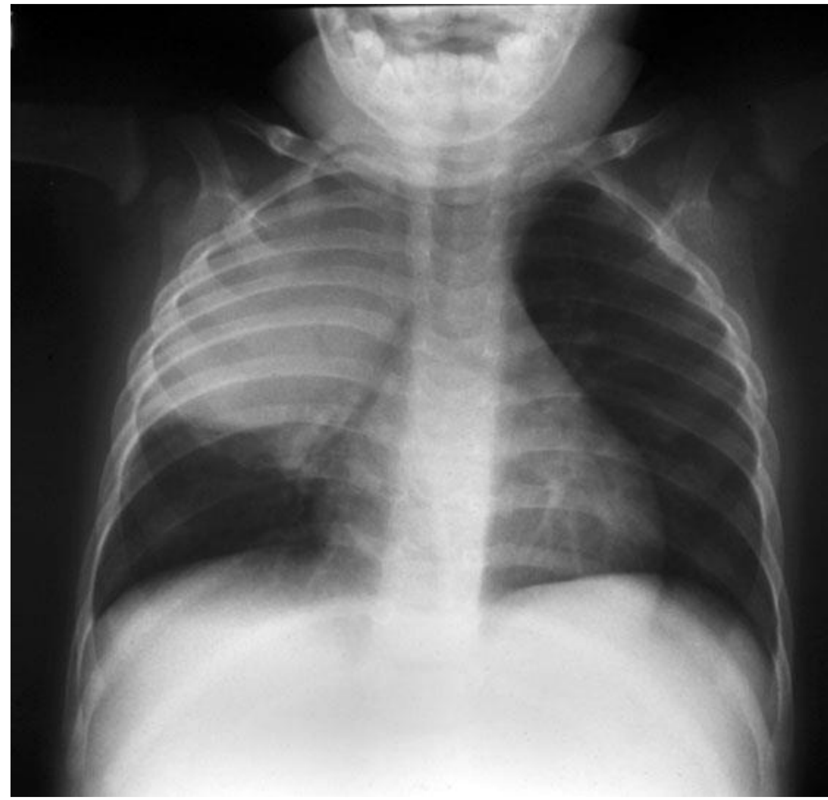
Pulmonary Disease

- Intrathoracic lymphadenopathy and parenchymal disease
- Progressive primary disease: Lung tissue destruction and cavity formation
- Reactivation disease: More common in adolescents

Tuberculosis: Chest X-Ray

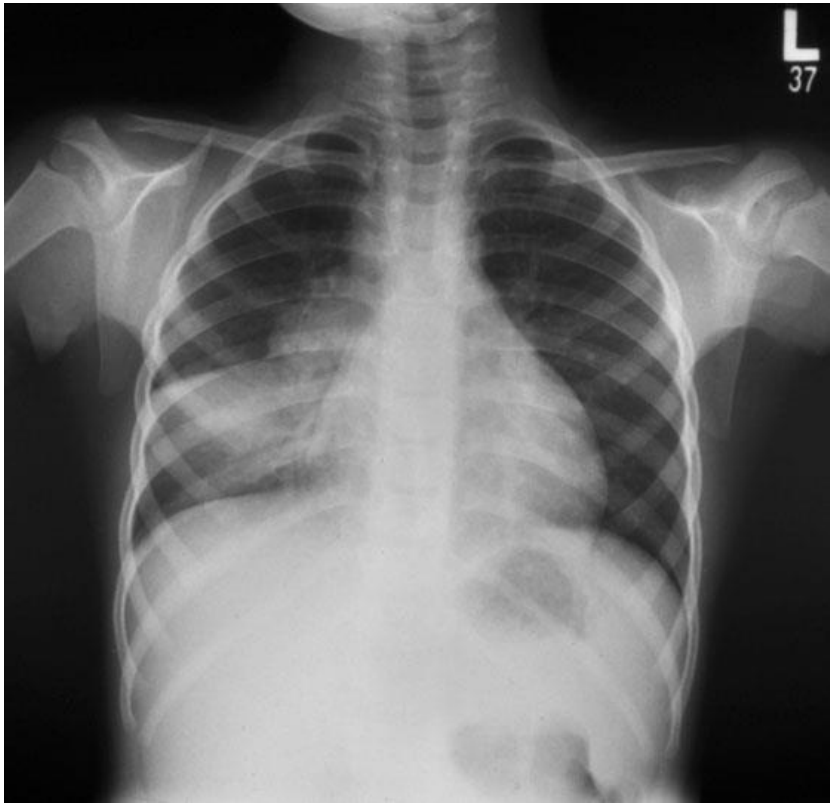


Miliary tuberculosis



Consolidation

Tuberculosis: Chest X-Ray



Consolidation

Cavitary lesion

Miliary Disease

- Younger or immunocompromised child
- Multiorgan involvement is common
- Most affected children have constitutional symptoms, hepatosplenomegaly
- CNS involvement: Up to 20% of children
- TST: Insensitive (TST anergy)
- AFB culture from gastric aspirates: Yield as high as 50%

Are children with TB ever contagious?

- Difficult to answer in the community
- Orphanages – caretaker with TB led to transmission; a child with TB did not
- Schools – only 2 reported "epidemics" caused by children <13 years old
- Children's Hospitals – rare case reports of transmission, all with special circumstances, none has been patient - to - patient

Features of Contagious Pediatric Tuberculosis

- Cavitary lung lesion
- Sputum production
- Positive acid-fast stain of sputum smear
- Bronchoscopy
- Draining lesions or surgical drainage of an abscess

Diagnosis

- Tuberculin skin test
- T-cell assays (IGRA): Measure IFN-γ released by sensitized T-lymphocytes after stimulation by antigens
- Laboratory diagnosis
  - Culture
  - Molecular amplification methodology: PCR, GeneXpert MTB/RIF

Tuberculin Skin Test

- False-positive TST result: Children exposed to non-tuberculous mycobacteria, recently received BCG vaccine
- False-negative TST result: Recent measles infection, high-dose corticosteroid, irradiation, immunosuppressive therapy, or immunocompromising conditions

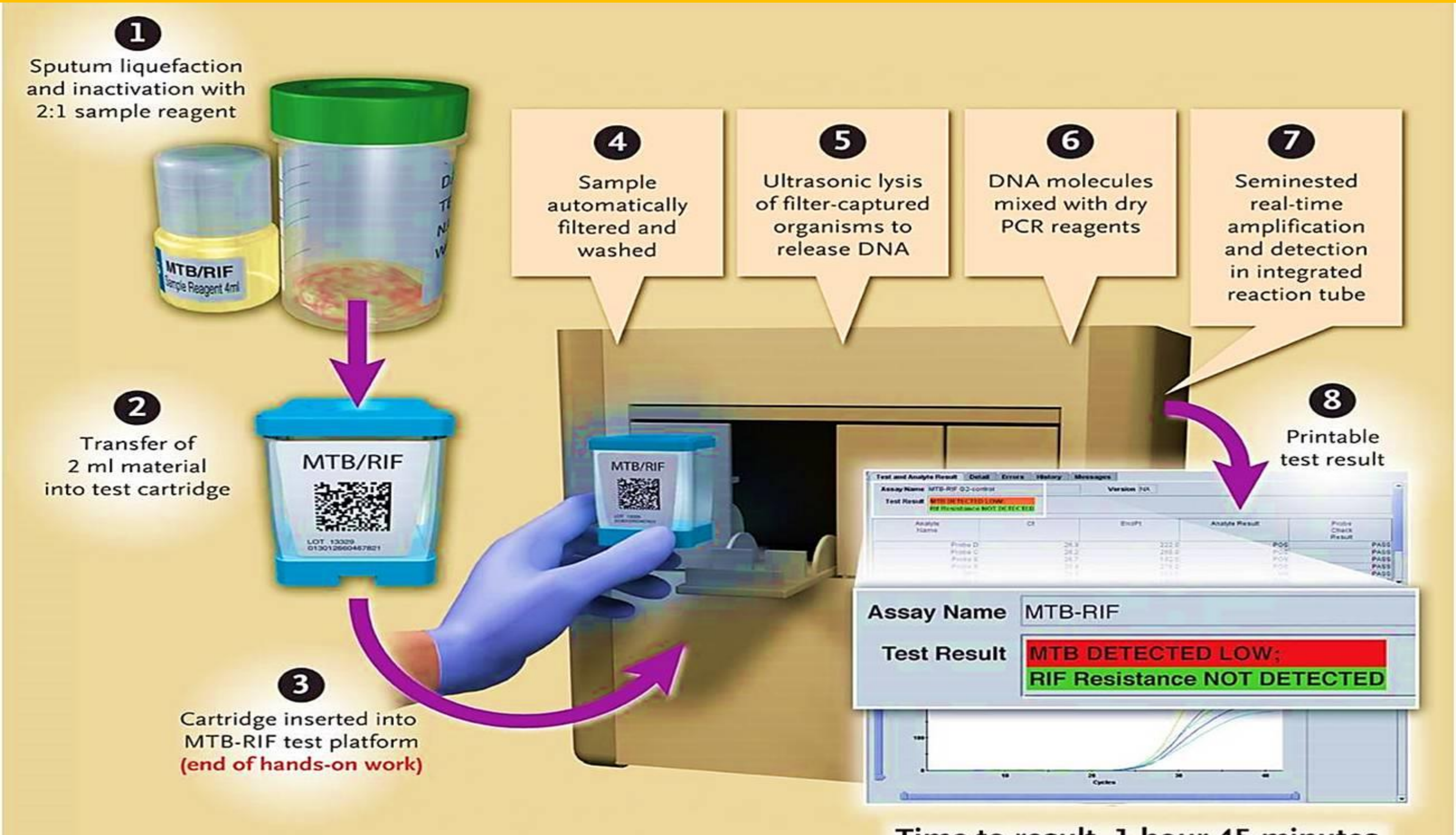
Interferon-Gamma Release Assays (IGRAs)

- Unable to distinguish between active disease and latent tuberculosis infection
- For immunocompetent children, IGRAs can be used in place of a TST to confirm cases of TB or LTBI, likely will yield fewer false-positive test
- Higher specificity than TST: Antigens used are not found in BCG or most pathogenic non-TB mycobacteria (eg, are not found in *M. avium* complex but are found in *M. kansasii*, *M. fortuitum*, and *M. marinum*)

Culture

- Most important laboratory test for the diagnosis and management of TB
- Positive of cultures from early-morning gastric aspirates from children with pulmonary TB is <40%
- Culture is most important when the source case is unknown or is known to have drug-resistant TB

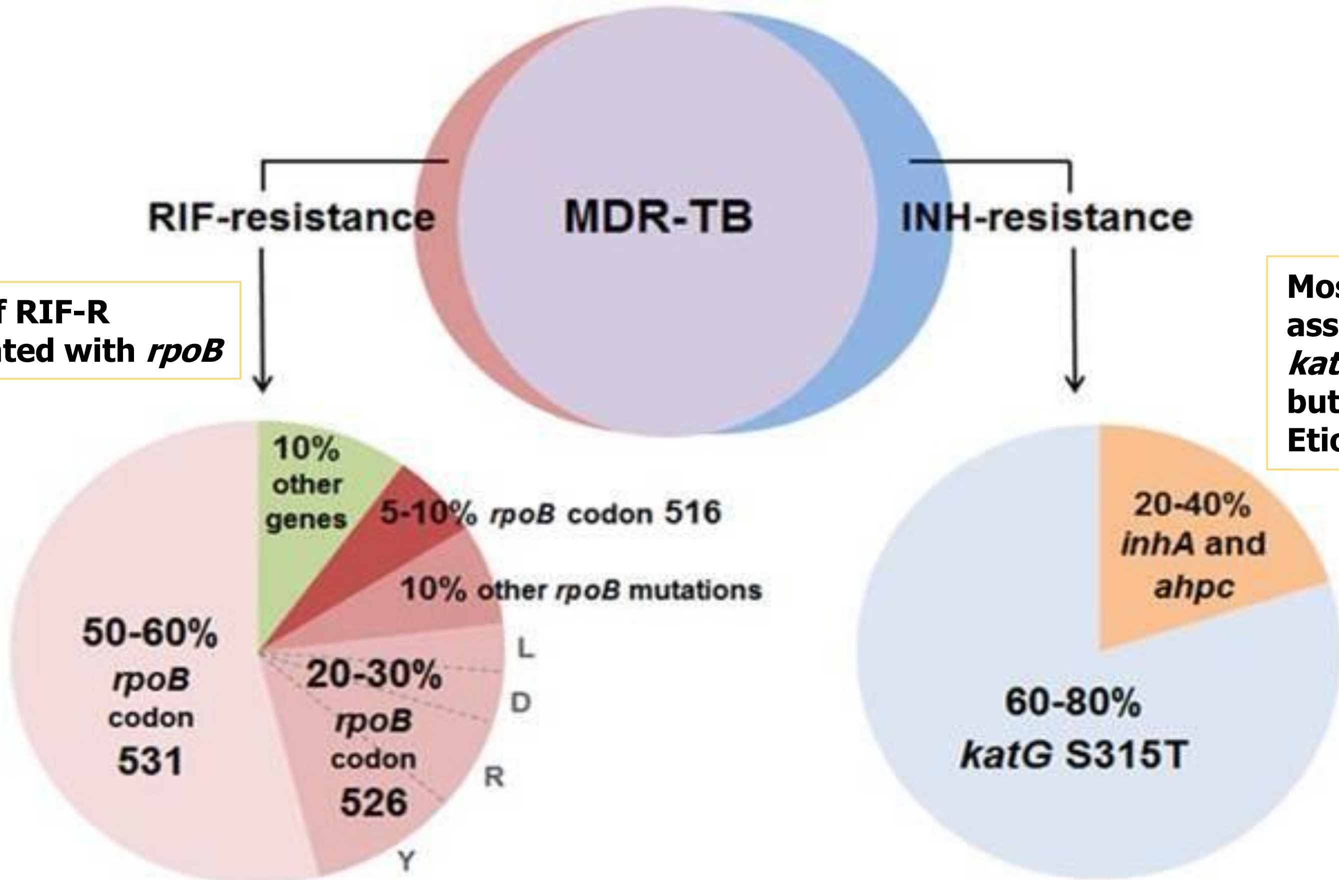
GeneXpert MTB/RIF



N Engl J Med 2010; 363:1005-1015.

Distribution of MDR-TB determining mutations

90% of RIF-R associated with *rpoB*



Most of INH-R associated with *katG*: high level-R but not cross to Etionamide

Rapid Molecular Detection of Multidrug-Resistant Tuberculosis by PCR-Nucleic Acid Lateral Flow Immunoassay

PLoS ONE 2015; 10(9): e0137791.

Treatment of Drug-Susceptible TB

Sites/Characteristics of TB Diseases	Treatment Regimens
Pulmonary, lymph node	2 IRZE/4-7 IR
Bone/joint, CNS, miliary	2 IRZE/10 IR
CNS, miliary, pericadium, pleural, endobronchial	Add prednisolone 1-2 MKD for 4-6 weeks

แนวทางปฏิบัติ วัณโรคในเด็ก 2562 สมาคมโรคติดเชื้อในเด็กแห่งประเทศไทย

Infectious Diarrhea

Pathogens

- Bacteria: *Salmonella*, *Shigella*, *Vibrio cholerae*, *Clostridium perfringens*, *S. aureus,* Shiga toxin-producing *E. coli*, *Yersinia*, *Vibrio parahemolyticus*, *Vibrio vulnificus*, *Campylobacter*, *Clostridium difficile*, *Aeromonas*, *Plesiomonas shigeloides*
- Virus: Rotavirus, Norwalk agent, calicivirus, adenovirus, astrovirus, coronavirus
- Parasites: *Entamoeba histolytica*, *Giardia lamblia*, *Cryptosporidium parvum*, *Isospora belli*, *Blastocystis hominis*, *Microsporidium*

Invasive Bacterial Diarrhea

- Caused by infection due to pathogens having an ability to invade the mucosa of the distal small intestine and colon
  - *Shigella* spp.
  - *Salmonella* spp.
  - *Campylobacter* spp.
  - *E. coli*

Acute Diarrhea: Antimicrobial Treatment

- Antimicrobial therapy is not usually indicated in children.
- Antimicrobials are reliably helpful only for children with bloody diarrhea (most likely shigellosis) and suspected cholera with severe dehydration.
- Antiprotozoal drugs can be very effective for diarrhea in children, especially for *Giardia, Entamoeba histolytica*, and now *Cryptosporidium*, with nitazoxanide.

Acute Diarrhea: Empirical Antimicrobial Treatment

- Antimicrobial therapy should be considered for severe invasive diarrhea (acute onset of bloody/mucous diarrhea or fecal polymorphonuclear leukocytes with high fever)
- Suspected septicemia or complications

Shigellosis

- Most common cause of dysentery
- Generally self-limited course, diarrhea usually resolves within 5-7 days
- Antimicrobial therapy is effective in shorten duration of diarrhea and hastening eradication of organisms from feces
- Most strains are resistant to ampicillin, TMP/SMX and nalidixic acid
- For cases in which treatment is required and susceptibility is unknown, azithromycin, ceftriaxone, or a fluoroquinolone should be administered[1]

1. Red Book: 2018 Report of the Committee on Infectious Diseases. 31st ed.

Antibiotics for treating salmonella gut infections (Review)

Sirinavin S, Garner P

THE COCHRANE COLLABORATION®

Authors' conclusions

There appears to be no evidence of a clinical benefit of antibiotic therapy in otherwise healthy children and adults with non-severe salmonella diarrhoea. Antibiotics appear to increase adverse effects and they also tend to prolong salmonella detection in stools.

Cochrane Database Syst Rev. 2000;(2):CD001167

Salmonella Infections

- Antimicrobial therapy may be recommended for gastroenteritis caused by nontyphoidal *Salmonella* serotypes in people at increased risk of invasive disease (eg. age <3 months, patients with chronic gastrointestinal tract disease, malignant neoplasms, hemoglobinopathies, HIV infection, or other immunosuppressive illnesses or therapies)

1. Red Book: 2018 Report of the Committee on Infectious Diseases. 31st ed.

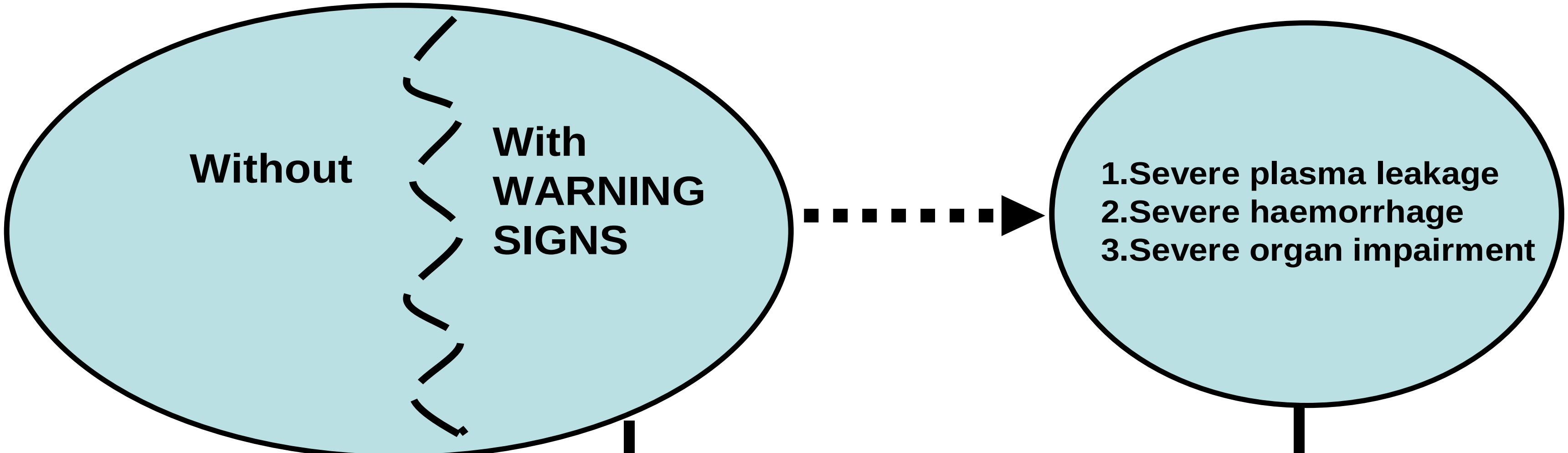
Dengue Fever / Dengue Hemorrhagic Fever

Dengue Virus Infection

- Dengue viruses: 4 serotypes
- Transmission: *Aedes aegypti*, *Aedes albopictus*
- Each serotype produces type-specific immunity but not immunity against other types

Revised Dengue Classification: WHO 2009

DENGUE ± Warning Signs **SEVERE DENGUE**



Probable Dengue
Live in / travel to dengue endemic area. Fever and 2 of the following criteria:
- Nausea, vomiting
- Rash
- Aches and pains
- Tourniquet test +ve
- Leucopenia
- Any warning sign

Lab. confirmed dengue
(important when no sign of plasma leakage)

Warning Signs*
- Abdominal pain or tenderness
- Persistent vomiting
- Clinical fluid accumulation
- Mucosal bleed
- Lethargy; restlessness
- Liver enlargement >2cm
- *Laboratory:* Increase in HCT concurrent with rapid decrease in platelet count

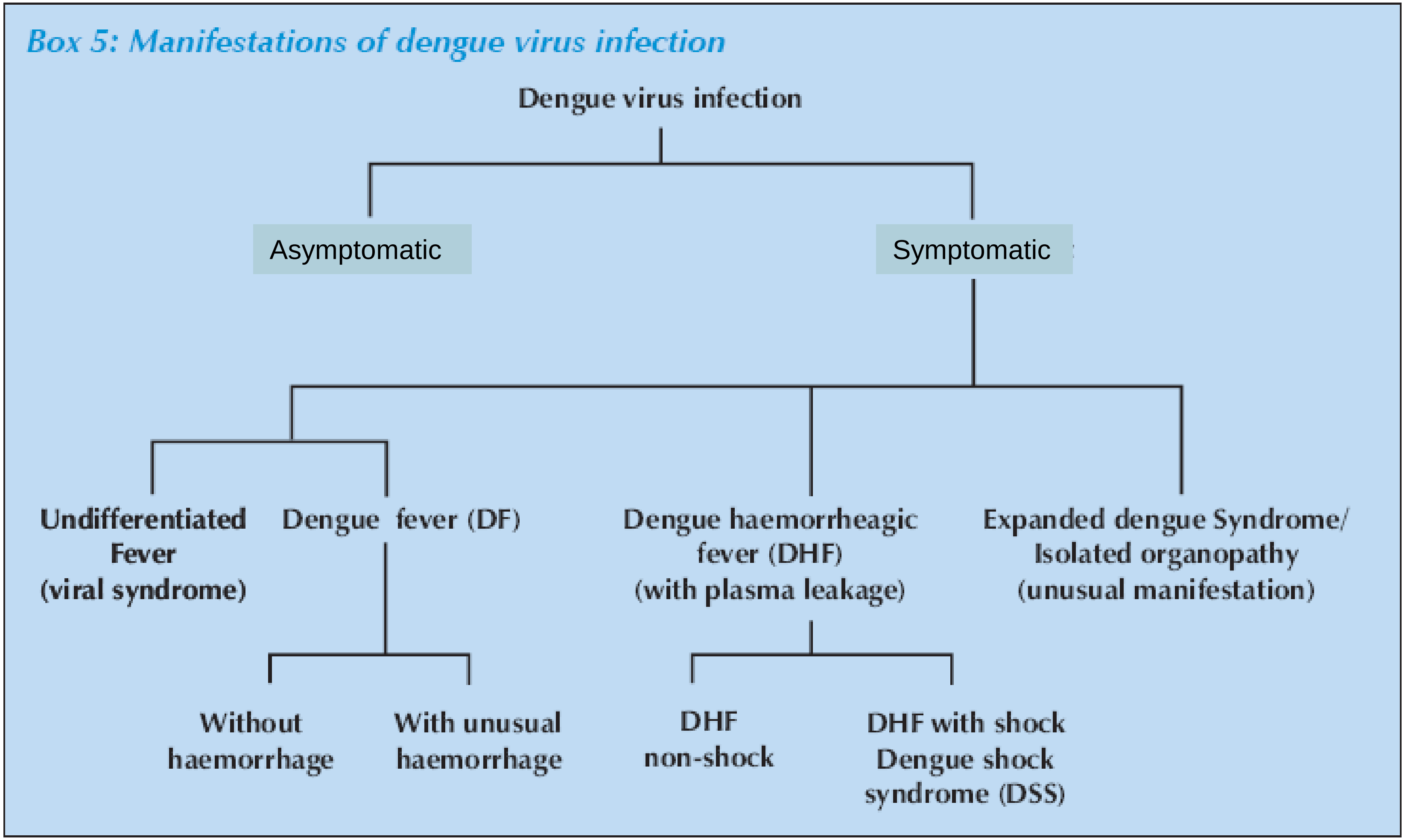
1. Severe plasma leakage leading to
- Shock (DSS)
- Fluid accumulation with respiratory distress

2. Severe bleeding
as evaluated by clinician

3. Severe organ involvement
- *Liver:* AST or ALT>=1000
- *CNS:* Impaired consciousness
- *Heart and other organs*

***** Requiring strict observation and medical intervention***

Dengue Classification: WHO SEARO 2011



WHO Regional Office for Southeast Asia. Comprehensive guidelines for prevention and control of dengue and dengue haemorrhagic fever. Revised and expanded version. SEARO Technical Publication Series, New Delhi, India 2011.

Dengue Virus Infection: Treatment

- No specific treatment
- Supportive treatment
  - Oral or IV fluid rehydration
  - Avoid use of aspirin, and other NSAIDs to minimize the potential for bleeding
  - Blood transfusion: In patients with significant bleeding
  - Platelet transfusions: In patients with severe thrombocytopenia ($<10,000/mm^3$) and active bleeding
- Adjunctive therapy
  - Meta-analysis of 4 trials found that corticosteroids were no more effective than placebo in reducing the number of deaths, the need for blood transfusion, or the number of serious complications[1]

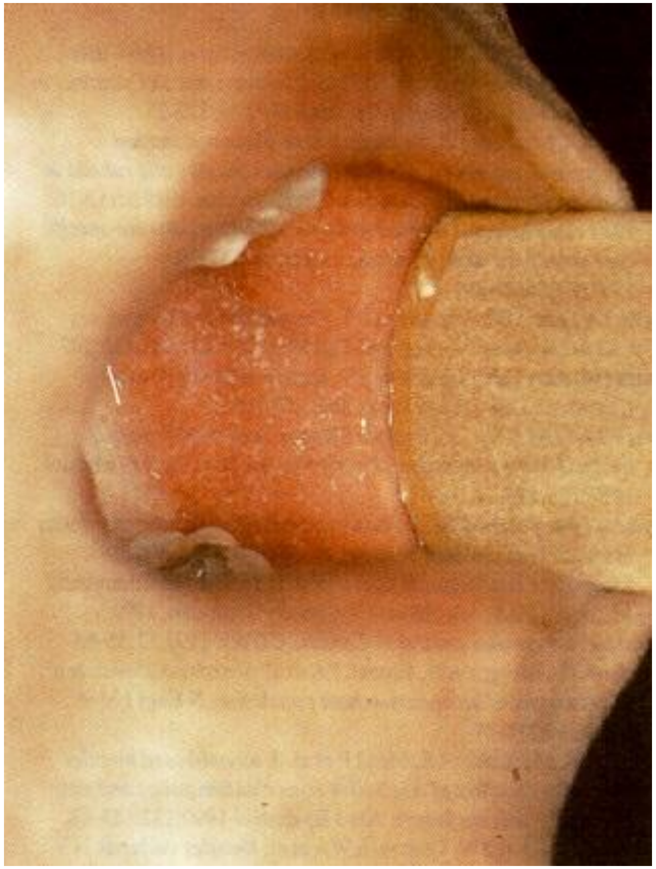
1. Panpanich R, et al. *Cochrane Database Syst Rev*. 2006;CD003488.

Measles

- High fever, cough, conjunctivitis, and coryza followed by the development of rash
- Rash: morbilliform, blanching rash, which begins on the face and spreads cephalocaudally and centrifugally to involve the neck, upper and lower aspect of the trunk, and extremities 2 to 4 days after onset of fever

Measles

- Koplik spots, guttate minute white macules on the buccal mucosa: Pathognomonic



Measles elimination by 2020

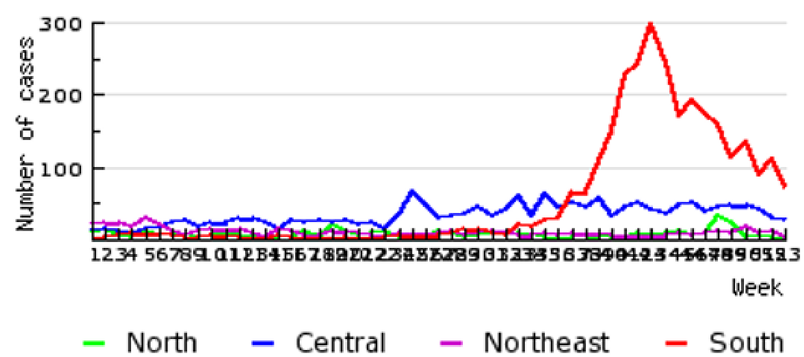
- **ภูมิภาคเอเชียตะวันออกเฉียงใต้ซึ่งมีไทยเป็นหนึ่งใน 11 ประเทศสมาชิก ได้มีข้อตกลงในการประชุมสมัชชาองค์การอนามัยโลก ครั้งที่ 63 ได้ตั้งเป้าหมายกำจัดโรคหัด ใน พ.ศ.2563**
- WHO's South-East Asia Region 11 Member States: Bangladesh, Bhutan, Democratic People's Republic of Korea, India, Indonesia, Maldives, Myanmar, Nepal, Sri Lanka, Thailand and Timor-Leste

World Health Organization
Regional Office for South-East Asia

Epidemiology of Measles in Thailand (2018)

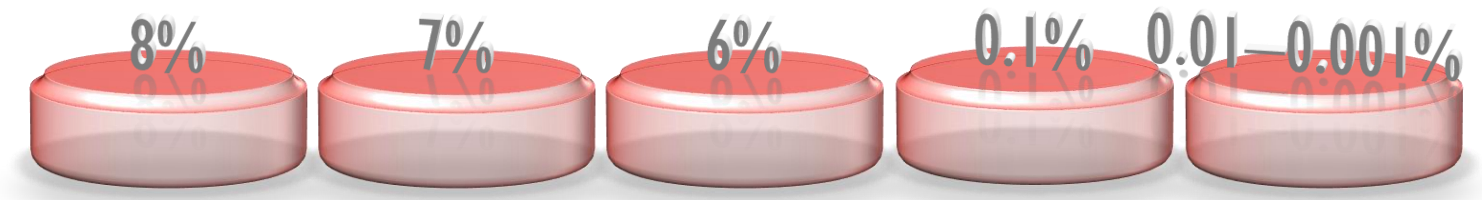
- Incidence 5,642 cases
  (8.62 /100,000 populations)
- Death 11 cases
- Most common age group:
  : 15-24 years (18.34%),
  : 25-34 years (15.99%) and
  : 1 years (9.22%)

Number of Measles cases by week of onset and region. 2561



Potential complications associated with measles

- Potential complications vary in frequency and severity:[1–3]



Diarrhea[1] | **Otitis media[1]** (mainly children) | **Pneumonia[1]** | **Encephalitis[1]** (high case mortality) | **SSPE*[2,3]**

- In developing countries, measles can be worsened by malnutrition, vitamin A deficiency and simultaneous infections[1,2,4]
  - Persistent diarrhoea, deafness and blindness can also occur[2,4,5]

* SSPE, subacute sclerosing panencephalitis

[1]CDC *Epidemiology and prevention of vaccine-preventable diseases* 2012; [2]WHO *Wkly Epidemiol Rec* 2009; 84: 349–60; [3]Campbell *et al*. *Int J Epidemiol* 2007; 36: 1334–48; [4]Whittle, Aarby. *Oxford Textbook of Medicine* 4th ed 2003; 351–7; [5]Dunmade *et al*. *J Deaf Stud Deaf Educ* 2007; 12: 112–8

Measles: Diagnosis

- Diagnosis of measles virus should be performed
  - IgM antibodies: High sensitivity and specificity
  - RT-PCR: High specificity but low sensitivity

Measles: Treatment

- In developing countries where the morbidity and mortality associated with measles are high, administration of vitamin A to children with active measles decreases measles complications such as diarrhea and pneumonia[1-3]
- Vitamin A can function as an immunomodulator by boosting antibody responses to measles[4-6]

1. Coutsoudis A, et al. *Pediatr Infect Dis J.* 1992;11:203-9.
2. Hussey DG, Klein M. *N Engl J Med*. 1990;323:160-4.
3. Sommer A. *J Infect Dis*. 1993;167:1003-7.
4. Cantorna MT, et al. *J Immunol*. 1994;152:1515-22.
5. Mora JR, et al. *Nat Rev Immunol*. 2008;8:685-98.
6. Ross AC. *Proc Soc Exp Biol Med*. 1992;200:303-20.

Measles: Treatment

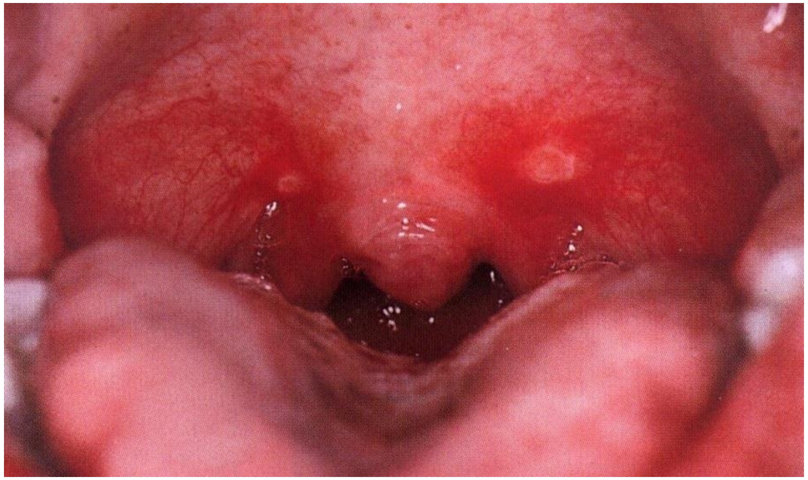
- Populations at increased risk for complications
  - Children hospitalized 6 months to 2 years of age
  - Older than 6 months with immunodeficiency
  - Evidence of vitamin A deficiency
  - Impaired intestinal absorption
  - Moderate to severe malnutrition

Measles: Vitamin A Treatment

- WHO currently recommends vitamin A for all children with acute measles, regardless of their country of residence.
- Vitamin A treatment: Once daily for 2 days
  - 200,000 IU for children 12 months or older
  - 100,000 IU for infants 6 through 11 months of age
  - 50,000 IU for infants younger than 6 months
- An additional (ie, a third) age-specific dose should be given 2 through 4 weeks later to children with clinical signs and symptoms of vitamin A deficiency

Hand, Foot and Mouth Disease: Complications

- Brainstem encephalitis
- Myocarditis

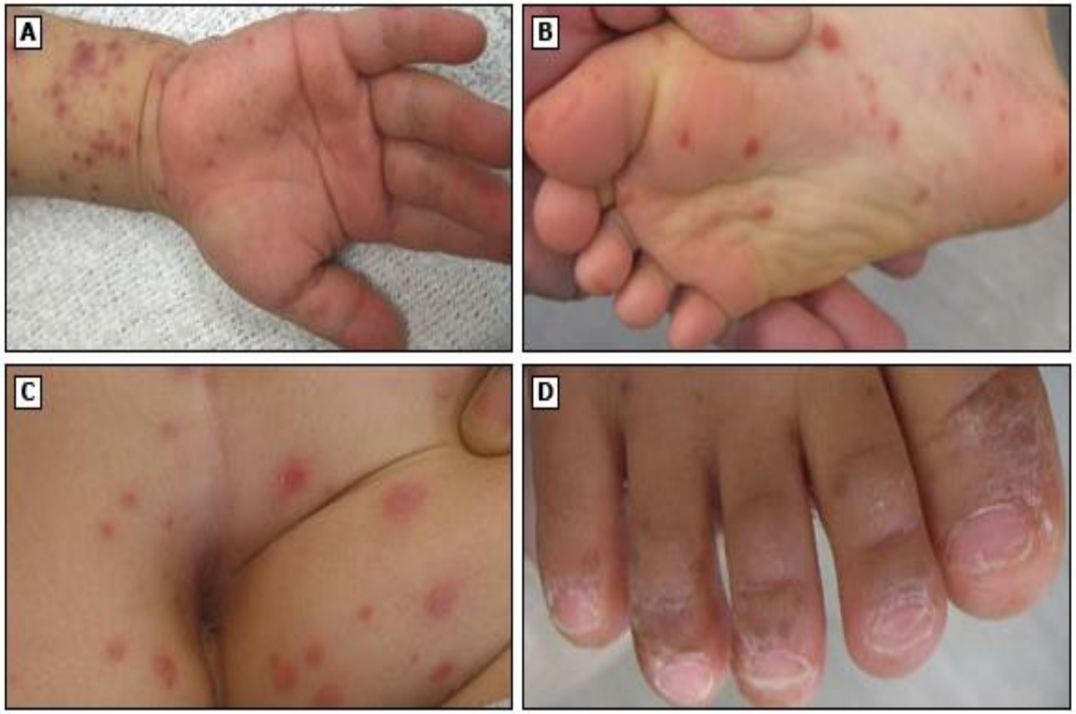


Coxsackie Virus

- CV-A16: Classic HFMD
- CV-A6: Atypical HFMD, associated with widespread, severe vesiculobullous disease, localization to areas of atopic dermatitis (so-called eczema coxsackium), high rates of onychomadesis, and a perioral eruption, unlike CV-A16.

- Increasing reports of HFMD in adults caused by the more virulent CV-A6

HFMD: CV-A6



Reproduced from: Fujimoto T, et al. Emerg Infect Dis 2012; 18:337.

HFMD: CV-A6 infection in adults

Reproduced from: Banta J, et al. MMWR Morb Mortal Wkly Rep 2016; 65:678.

Herpes Simplex Encephalitis (HSE)

- Usually caused by HSV type 1
- Fever, confusion, seizures
- Diagnosis
  - MRI of the brain – Temporal lobe involvement
  - EEG: Periodic lateralized epileptiform discharges
  - Positive HSV PCR from CSF

Neonatal HSV Infection

Route of Infection	%
In Utero	5
Intrapartum	85
Postpartum	10

Neonatal HSV Infection

Disease	%
Disseminated disease - DIC - Pneumonia - Hepatitis - CNS involvement (60-75%)	~25
Encephalitis (CNS disease) - Seizures - Lethargy - Irritability - Poor feeding - Temperature instability	~30
Skin, eyes, and/or mouth (SEM disease)	~45

Neonatal HSV Disease

Diagnosis of Neonate Born to Maternal Active Genital Herpes Lesions

At 24 hours of age obtain from the neonate:

- HSV surface cultures (and PCRs if desired)
  - Swabs of mouth, nasopharynx, conjunctivae, anus
- HSV blood PCR
- CSF cell count, chemistries, and HSV PCR
- Serum ALT

Red Book: 2018 Report of the Committee on Infectious Diseases, pp. 437-49.

Neonatal HSV disease

- Delivery by cesarean section is recommended if active genital lesions are present at the end of pregnancy
- Treatment: IV acyclovir 60 mg/kg/day for 14 days in SEM disease and for 21 days in CNS disease or disseminated disease
- Oral acyclovir suppressive therapy for 6 months may improve neurodevelopmental outcomes in neonatal HSV disease with CNS involvement[1]

1. Kimberlin DW, et al. *N Engl J Med*.2011;365:1284-92.

Varicella Zoster Virus

- Primary infection: Chickenpox
  - Incubation period: 14-16 days, occasionally 10-21 days
- Recurrent disease: Herpes zoster
  - Associated with aging, immunosuppression, intrauterine exposure, varicella at <18 mo of age

In Utero Varicella Infection

Pregnancy	Neonatal Outcomes
Before 20 weeks (1st or early 2nd trimester)	Fetal death, congenital varicella syndrome (1-2%) (limb hypoplasia, cutaneous scarring, eye abnormalities)
After 20 weeks (3rd trimester to 21 days before delivery)	Can develop zoster early in life without varicella
Perinatal • 6-21 days before delivery - GA >28 weeks - GA <28 weeks • 5 days before to 2 days after delivery	 • Passive VZV Ab • No passive VZV Ab • Neonatal varicella (untreated mortality rate 30%)

Varicella: Treatment

- Oral acyclovir is not recommended for routine use in otherwise healthy children with varicella
- Oral acyclovir should be considered for otherwise healthy people at increased risk of moderate to severe varicella
  - Age >12 years
  - Chronic cutaneous or pulmonary disorders
  - Receiving long-term salicylate therapy
  - Receiving short, intermittent, or aerosolized courses of corticosteroids

Varicella: Treatment

IV acyclovir: Indication

- Immunocompromised patients including chronic corticosteroids

Zika Virus

- Arthropod-borne flavivirus transmitted by *Aedes* mosquitoes
- Clinical manifestations of Zika virus infection occur in approximately 20% of patients and include acute onset of low-grade fever with maculopapular rash, arthralgia (notably small joints of hands and feet), or conjunctivitis (nonpurulent)

Zika Virus: Intrauterine Infection

- Intrauterine Zika virus infection in pregnant women has been associated with microcephaly and fetal loss (in the first trimester)[1]

1. Meaney-Delman D, et al. *Obstet Gynecol.* 2016; 127:642.

Zika Virus: Intrauterine Infection

- Retrospective analysis from French Polynesia estimated a baseline microcephaly prevalence of 2 cases per 10,000 neonates and risk of microcephaly associated with Zika virus infection rate of 95 cases per 10,000 women infected in the first trimester[1]

1. Cauchemez S, et al. *Lancet* 2016.

Zika virus and Microcephaly

Studies of Guillain–Barré Syndrome or Microcephaly in Association with Zika Virus Infection, According to Study Design and Date of Publication.*

Study Type	Countries (Yr of Publication)	No. of Studies	Main Findings	Strengths	Weaknesses
Microcephaly					
Ecologic	Brazil: Paraíba, Bahia (2016)	2	Paraíba: retrospective review 2012–2015: 16,208 births; higher-than-expected (2–8%) incidence of microcephaly; Bahia: ecologic association between reports of acute rash, March–June 2015 and microcephaly cases October 2015–January 2016	Temporal associations; large number of births; Bahia data suggest association with late first and early second trimester	Ecologic associations only; no confirmed Zika cases; alternative explanations not excluded
Case reports or case series	French Polynesia (2015)	1	Retrospective review of 2013–2014 Zika outbreak period: 17 cases of congenital brain malformations, including microcephaly	Temporal association with Zika outbreak; other congenital brain abnormalities observed	No documented maternal infection; retrospective; most not tested for ZIKV; no control group
Case reports or case series	Brazil: several states (2015–2016)	11	93 Cases of microcephaly, 70 with history of maternal symptoms (laboratory-confirmed in 1 of 3 tested); 9 with ZIKV in amniotic fluid, fetal or neonatal brain; 4 with ZIKV in brain but not other organs	Biologic evidence of ZIKV in fetal or neonatal brain tissues and neurotropism	Most maternal ZIKV exposures were self-reported; other congenital infections not always excluded; no control group
Case reports or case series	Various countries (2016)	1	9 Women returning to United States from Zika-affected countries, August 2015–February 2016; all reported symptoms, all laboratory-confirmed recent ZIKV infection; 2 early pregnancy losses, 2 terminations, 1 microcephaly, 2 healthy newborns, 2 still pregnant	Temporal association; biologic evidence of maternal ZIKV infections	Alternative explanations not excluded; no control group
Cohort study	Brazil: Rio de Janeiro (2016)	1	88 Women with rash during pregnancy, 72 ZIKV-positive on RT-PCR; ultrasound normal in all 16 ZIKV-negative women; ultrasound abnormal in 12 of 42 ZIKV-positive women at all stages of pregnancy (29%); microcephaly mostly in association with intrauterine growth restriction	Temporal association; biologic evidence; strong association with abnormal ultrasound or neonatal outcome	Small study; control group presumed to have other causes for rash; some congenital infections not excluded

Broutet N, et al. *N Engl J Med*. 2016;374:1506-9.

Zika Virus Infection

- Neurotropism of Zika virus has been demonstrated in vivo and in vitro[1-4]
- Zika virus infection has been associated with neurologic complications[5]
  - Congenital microcephaly
  - Developmental problems among babies born to infected pregnant women
  - Guillain-Barré syndrome
  - Myelitis
  - Meningoencephalitis
  - Acute disseminated encephalomyelitis (ADEM)

1. Tang H, et al. *Cell Stem Cell.* 2016.
2. Mlakar J, et al. *N Engl J Med.* 2016; 374:951.
3. Nowakowski TJ, et al. Cell Stem Cell. 2016.
4. Sirohi D, et al. Science. 2016.
5. WHO. Emergencies: Zika situation report. http://www.who.int/emergencies/zika-virus/situation-report/31-march-2016/en/ (Accessed on April 01, 2016).

Laboratory testing for Zika virus infection in the neonate

- Serum and urine for Zika virus RNA via real-time reverse transcription PCR (rRT-PCR).
- Serum Zika virus IgM enzyme-linked immunosorbent assay (ELISA).
- If CSF is available, test CSF for Zika virus RNA (via rRT-PCR) as well as Zika virus IgM

ขอบคุณครับ