SARI CLINICAL CARE TRAINING

ANTIMICROBIAL THERAPY AND ITS MODIFICATION AFTER DIAGNOSTIC TEST INTERPRETATION

World Health Organization

HEALTH EMERGENCIES programme

Learning objectives

At the end of this lecture, you will be able to:

- Prescribe empiric antimicrobial therapy to patients with SARI and suspected severe pneumonia/sepsis.
- Describe antiviral therapy for influenza infection
- Describe antiviral therapy for patients with COVID-19 infections.
- Understand how to interpret diagnostic test results and modify management.

Prescribing antimicrobial therapy for patients with SARI (1/3)

- Give appropriate, empiric broad-spectrum antimicrobials **as soon as possible** of recognition of patient with SARI and sepsis/severe pneumonia (in the emergency area when possible).

- Preferably after the clinical specimen collection (upper and/or lower respiratory samples and blood cultures).

- Each hour delay in administration of effective antimicrobial therapy in septic shock is associated with increased mortality.

Prescribing antimicrobial therapy for patients with SARI (2/3)

- Empiric therapy may include one or more effective drugs to treat **all** likely pathogens:
  - i.e. antibiotics for suspected bacterial pathogens, antiviral for suspected viral pathogen (if effective antiviral is known), antifungal for suspected fungal pathogen, etc.).

- For patients with septic shock, can consider combination therapy:
  - i.e. using two antibiotics of different antimicrobial classes aimed at most likely bacterial pathogen.

Antivirals for COVID-19

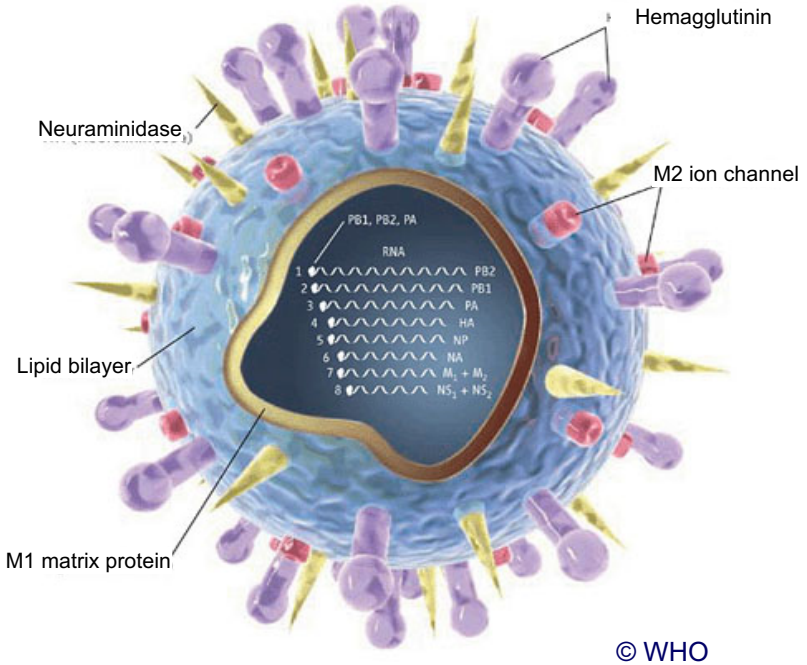
- There are no known effective antivirals for coronavirus infections.
- Various candidates with potential anti-nCoV activity are being evaluated for clinical trial protocols (see module 15).
- Use of unregistered or unproven therapeutics for nCoV should be done under strict monitoring and ethical approval.
  - Use WHO Monitored Emergency Use of Unregistered Interventions (MEURI) framework (see module 15)

Prescribing antivirals for patients with influenza virus infection

- For patient with or at risk of severe seasonal influenza A or B viruses or those with zoonotic influenza A virus infection:
  - Give antiviral (NAI, oseltamivir) as soon as possible.
    - earlier treatment has greater clinical benefit than later treatment or no treatment.
  - Can give at any stage of active disease when ongoing viral replication is anticipated or proven.
  - Influenza viral replication can be prolonged in the lower respiratory tract in critically ill patients.

Pharmacology of antiviral agents for influenza

- Neuraminidase inhibitors:
  - **oseltamivir (including Tamiflu™, Antiflu™)**
  - zanamivir inhaler(including Relenza™), IV formulation is investigational drug
  - peramivir (including Rapivab™).



Pharmacology: antiviral susceptibility of human infection with influenza viruses, January 2020

	Oseltamivir	Zanamivir	M2 inhibitors
Seasonal A (H1N1) pdm09	Susceptible*	Susceptible	Resistant
Seasonal A (H3N2)	Susceptible	Susceptible	Resistant
Influenza B	Susceptible	Susceptible	Resistant
Avian influenza A (H5N1)	Susceptible	Susceptible	Variably resistant
Avian influenza A (H7N9)	Susceptible	Susceptible	Resistant

*Sporadic community isolates resistant to oseltamivir have been reported. Resistant variants have emerged during therapy for oseltamivir for all of the listed viruses (and very rarely for zanamivir).

Prescribing oseltamivir (1/2)

- **WHO recommends for patient with severe or at risk for severe, seasonal influenza virus infection and zoonotic influenza virus infection.**

- Oral capsule or suspension, that can be given via nasogastric or orogastric tube in ventilated patients.

- Dose is 75 mg twice daily for **5 days** in adults

Give as soon as possible to patient with suspected or confirmed influenza virus infection of all ages.

Prescribing oseltamivir (children) (2/2)

- Dose in children up to 40 kg is 3 mg/kg twice daily for **5 days**
- Dose in children over 40 kg is adult dose (75 mg twice daily for **5 days**)
- Available as oral suspension (6 or 12 mg/mL) and tablets (30 mg, 45 mg, 75 mg)

Intravenous neuraminidase inhibitors

- IV peramivir:
  - Approved for use in China, Japan, Republic of Korea and United States of America for treatment of **uncomplicated influenza** in outpatients via a single infusion.

- IV zanamivir:
  - Recent clinical trial found IV zanamivir at 600 mg once daily **not superior to oseltamivir in hospitalized adult** and adolescent patients.

WHO recommends against use of IV peramivir and IV zanamivir when compared to placebo for patients with severe or at risk for severe influenza infection. However, to be considered in patient with oseltamivir-resistant virus.

Interpretation of test results

- Detection of virus depends on multiple factors:
  - time of sample collection from illness onset
  - source of specimen (upper vs lower)
  - type of virus
  - diagnostic testing assay
  - storage and transportation conditions
  - host factors.

- Thus, there can be false negative results.

If you have a high clinical and epidemiologic suspicion of influenza, DO NOT stop treatment and IPC measures for influenza virus following a negative result. Repeat testing, sampling lower tract preferably.

Prescribing antibiotics therapy for patients with SARI

- Dose antimicrobials optimally based on pharmacokinetic principles:
  - i.e. take into account renal or hepatic function
  - i.e. take into account volume of distribution.

- Ensure drug adequately penetrates into tissue presumed to be source of infection (i.e. lungs):
  - e.g. gentamycin and daptomycin are not reliable CAP treatments in adults.

Choose the correct antibiotics (1/2)

- Patient's factors:
  - at risk for resistant pathogens (i.e. recent IV antibiotics)
  - at risk for opportunistic infections (i.e. immunosuppression, co-morbidities or presence of invasive devices).
- Epidemiologic factors:
  - Community acquired, hospital acquired, etc.
- Pathogen factors:
  - prevalent pathogens in community, hospital, etc.
  - susceptibility and resistance patterns of prevalent pathogens.

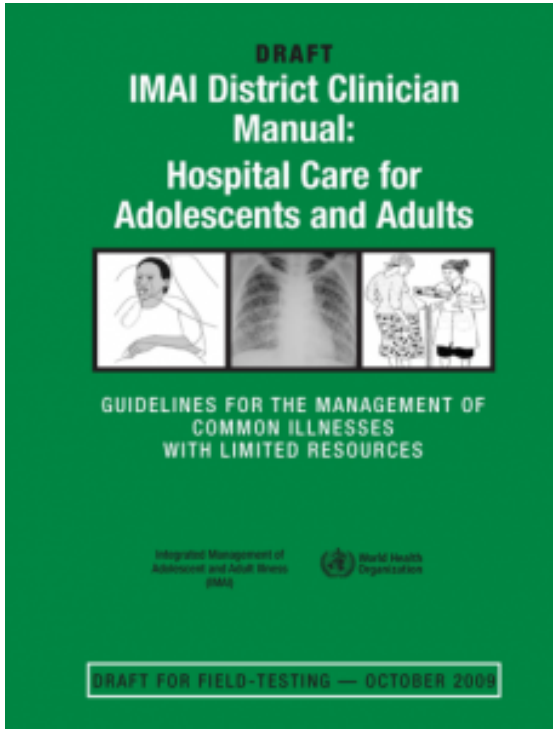
Choose the correct antibiotic (2/2)

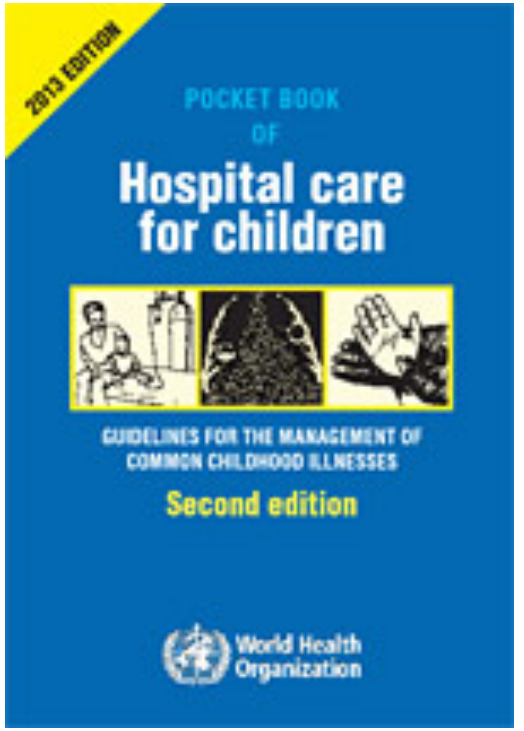
- Refer to local guidance for treatment recommendations:
  - based on local antibiograms.

- If none available, adapt international guidance:
  - Infectious Disease Society of America (IDSA):
    - CAP in adults published in 2007, revision pending
    - CAP in child older than 3 months of age, published 2011.
  - British Thoracic Society (BTS):
    - CAP in adults, published 2014.
  - NICE guidelines:
    - CAP in adults, published in 2015.

For limited-resource settings

WHO guidance





Examples of antibiotic regimens for severe CAP: IDSA and BTS guidelines

Combination therapy:

•*B-lactam* e.g. ampicillin-sulbactam, cefuroxime, cefotaxime or ceftriaxone

•**and** antibiotic against atypical pneumonia (e.g. macrolide or doxycycline) **or** respiratory flouroquinolone **(**e.g. levofloxacin).

If community-acquired methicillin-resistant *S. aur*eus (CA-MRSA) suspected:

•add vancomycin or linezolid.

If immunosuppressed (i.e. PL-HIV):

• consider anti-pneumocystis treatment (e.g. sulfamethoxazole/trimethoprim).

In pregnant women the use of macrolides, cephalosporins and penicillins are safe. Do not use flouroquinolones or doxycyline.

Paediatric recommendation from IDSA

Combination therapy:

•ampicillin or penicillin G for fully immunized child if local epidemiology documents **lack** of substantial high-level penicillin-resistance for invasive *S. pneumoniae.*

•**Or** third generation cephalosporin (e.g. cefotaxime or ceftriaxone) for non-fully immunized child, known high-level, penicillin-resistance for invasive *S. pneumoniae* or life-threatening infection.

And antibiotic against atypical pneumonia (i.e. macrolide).

If community-acquired *S. aur*eus suspected:

•add vancomycin or clindamycin based on local susceptibility data.

Flouroquinolones and doxycyline are not used to treat CAP in children.

Paediatric recommendation from WHO Child Handbook

Severe pneumonia:

•ampicillin or penicillin G + gentamicin.

If no signs of improvement within 48 hours:

• switch to third generation cephalosporin (e.g. cefotaxime or ceftriaxone).

If no improvement in 48 hours and suspect community-acquired *S. aureus:*

•switch to cloxacillin and gentamicin.

If HIV infection or exposure to HIV, suspect PjP pneumonia:

•child < 12 months, give high dose co-trimoxazole and sulfamethoxazole

•child 1–5 years, give PjP treatment only if clinical signs of PjP.

Flouroquinolones and doxycyline are not used to treat CAP in children.

Examples of antibiotic regimens for HAP from IDSA/ATS guidelines: 2016

Risk factors for MDR pathogen*:

•Prior intravenous antibiotic use within 90 days
•Admission from nursing home

Anti-pseudomonal coverage:

•cephalopsorin with antipseudomonal activity(e.g. ceftazidine, cefepime) **or**
•carbapenem (e.g. meropenem or imipenem **not** ertapenem) **or**
•B-*lactam/B-lactamase inhibitor* (e.g. piperacillin/tazobactam) **or**
•aztreonam (if penicillin allergic)
plus (double coverage can be considered if > 10% isolates are MDR)
•flouroquinolone (e.g. levofloxacin (high dose) or ciprofloxacin) **or**
•aminoglycoside (e.g. tobramycin, amikacin, gentamicin).

AND anti-methicillin-resistant *S. aureus* antibiotic if patient is at high risk of mortality (need for ventilator support due to pneumonia and sepsis) or > 20% isolates are MRSA:
•vancomycin or linezolid.

** Aliberti S et al. Clinical Infect Dose. 2012;54(4):470-478

Antimicrobial de-escalation (1/3)

- Re-assess the antimicrobial regimen daily for potential de-escalation.
- Narrow once causative agent is identified, sensitivities established:
  - continue most appropriate antimicrobial that targets the pathogen.
- In the absence of clinical or microbiological indication of bacterial infection consider discontinuation of antibiotics.

Antimicrobial de-escalation (2/3)

- If no causative agent, de-escalation should still occur, but strict criteria for de-escalation are not available.
- Considerations include:
  - signs of clinical improvement (i.e. once shock resolved)
  - signs of infection resolution (i.e. procalcitonin).
- 5–10 days of duration of treatment is adequate for most serious infections associated with sepsis.
- Longer treatment courses may be appropriate in patients with slow clinical response, undrainable foci and certain infections (i.e. *S. aureus* bacteremia).

Antimicrobial de-escalation (3/3)

Appropriate antibiotic use minimizes the risk of superinfection, drug resistance, adverse effects and costs.

Infectious disease consultation may be advisable if drug-resistant pathogens suspected or detected.

Reasons for clinical deterioration

Wrong antimicrobial treatment

- **Drug resistant pathogen**
- Pathogen not covered by antimicrobial regimen
- Inadequate potency of antimicrobial regimen

Complication-lack of source control

- Empyema, lung abscess, necrotizing infection, bronchopleural fistula
- Metastatic infection (CSF, endocarditis, osteomyelitis, septic arthritis)
- Hospital acquired infection (*C. difficille*, VAP)

Wrong diagnosis

- Non-infectious pneumonia
- Pulmonary embolism
- Cardiogenic edema
- Pneumothorax
- Drug fever
- Malignancy

Patient risk factors

- Immunosuppressed condition (i.e. HIV, cancer, chemotherapy recipient)
- Inadequate bioavailability of antimicrobial
- Underlying disease that impairs healing (i.e. diabetes)

Antiviral resistance in influenza

- Consider antiviral resistant influenza viruses, especially, if known to be circulating in the community:
  - notify appropriate public health officials
  - take serial respiratory samples and send to laboratory that can test for antiviral susceptibility
  - strictly adhere to IPC measures.
- Treat the patient with alternate antiviral, **such as IV zanamivir (on compassionate use basis).**

Immunomodulating agents

Corticosteroids and viral pneumonia

- Corticosteroid use is associated with various negative clinical outcomes, such as:
  - prolonged viral replication, avascular necrosis, promotion of immunosuppression leading to bacterial or fungal super-infection, psychosis, hyperglycaemia, and **increased mortality.**
- Consider its use only for specific indications such as exacerbation of asthma/COPD or suspected adrenal insufficiency or refractory shock or co-infection with PjP. If used, use only low dose.

There is NO proven role for corticosteroids
in acute influenza pneumonia or SARS/MERS infection.

Summary

- At this stage, there are no known antiviral therapies for COVID-19 infection. All therapeutics should be given, under strict monitoring and ethical approval, preferably randomized controlled trial.

- If influenza virus infection is suspected (i.e. seasonal influenza A or B viruses are known or suspected to be circulating among persons in the community or the patient is at risk for avian influenza A virus infection), then treat SARI patient empirically with oseltamivir,.

- SARI patients with sepsis or severe pneumonia, should also be treated with appropriate antibiotics as soon as possible with a clear de-escalation plan.

Acknowledgements

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