Date of writing: 13th May 2020

Self Study CME Series No.217 (1 CME Point)

Rational Use of Antibiotics in COVID-19 Pandemic

Ongoing battle against antimicrobial resistance (AMR) with limited supply of antibiotics

COVID-19 hits us in all walks of life. While we concentrate on finding a cure and vaccine for this novel infection, it is equally important that we do not lose sight on rational use of antibiotics[1]. Antibiotics are lifesaving for patients with cancer, dialysis, surgery, and many other treatment procedures. Prior to COVID-19, 700,000 deaths annually worldwide were caused by infection with drug-resistant organisms[2], which is almost three times the toll of COVID-19 so far; up to half of surgical site infections in developed countries are caused by drug-resistant microorganisms[3]. If no action is taken, mortality has been projected to 10 million per year by 2050 with economic loss comparable to the 2008 global financial crisis[4]. The pipeline of antibiotics has been dry due to the upside-down economics for antibiotic development: the less drugs people take, the better they work[5]. Five companies that brought new agents to market in past 3 years have gone bankrupt or left the field[2]. More than half of the new drugs in development are still in Phase 1 or 2 trials, taking them years for approval[6]. None of the candidates for treating the WHO-critical-threat pathogens is based on novel mechanism to safeguard against resistance development[7].

What is rational use of antibiotics?

We cannot just wait for new antibiotics to do our work. We need to continue practicing rational use of antibiotics to preserve their activities against targeted bacteria. Rational use means giving the right drug at the right time and right dose, for the right duration[8]; prescribe only as indicated and keep the course as short as possible. Benefits of responsible prescription includes fewer side effects for the patient, lower chance of emergence of resistance and reduced clinical workload in administering parenteral infusions[1]. Rational use is especially important at times when global supply of specific antibiotics may be disrupted due to shortages of raw materials and active pharmaceutical ingredients[2]. During COVID-19 pandemic, antibiotics should be viewed as crucial as masks and other personal protective equipment (PPE)[9].

Co-infections in viral pandemics

In a viral pandemic, antibiotics are mostly used to treat secondary bacterial infections. It is known that after influenza, *Streptococcus pneumoniae and Staphylococcus aureus* can cause secondary infections in about 35% and 28% respectively[10]. Other less common microbes include *Haemophilus influenzae, Streptococcus pyogenes, Pseudomonas aeruginosa* and fungi e.g. *Aspergillus*[10,11]. In fact, the vast majority of some 100 million deaths in the 1918 Spanish influenza was caused not by the virus itself but by secondary bacterial pneumonia[12]. Similarly, swine influenza (H1N1) in 2009 had up to 55% secondary infection rate[13] among the estimated deaths of 284,000[14].

In contrast, novel coronaviruses including SARS-CoV and MERS-CoV are not commonly associated with secondary bacterial infections[15]. For COVID-19 preliminary results show the rate to be low: In a rapid review of 18 reports of all types of coronavirus infection (50% on COVID-19, 28% on SARS, 6% on MERS, 17% on other coronaviruses), most studies (61%) did not identify bacterial/fungal co-infection. The study found that for COVID-19, rate of co-infections during hospitalization was 8% as compared to 11% for other coronaviruses[16]. The 'true' rate of co-infections for COVID-19 should be even lower if we discount fungal infections and hospital-acquired infections, which are strictly speaking nosocomial complications of prolonged ventilation instead of secondary infections per se[15]. For COVID-19 ventilator-associated infections should not be common given the small proportion of severe/critical cases (about 20%)[17]. Another notable feature is the rare occurrence of atypical bacteria co-infections (mycoplasma/legionella/chlamydia)[16]. Furthermore, the use of immunomodulatory agents e.g. tocilizumab for treatment of cytokine storms may carry unknown infective risk[2]. As the pandemic continues to evolve, more data on the relationship between SARS-CoV-2 and other pathogens are urgently required[18].

Characteristics of antibiotic use in COVID-19 patients

COVID-19 has caused a huge number of old and frail to be admitted to hospitals. The threshold of antibiotics for these patients is low because of high risk of deterioration. Covering the infection with empirical antibiotics is justified in initial phase as differentiation between viral and bacterial pneumonia is difficult, but the antibiotics prescription rate for COVID-19 patients appears exceedingly high at about 72%-95%[16,19]. One reason could be the overwhelming anxiety from the pandemic and the absence of antiviral treatment with proven efficacy[1]. Furthermore, diagnostic procedures that generate aerosols e.g. bronchoscopy and open suctioning of airways may be less frequently performed due to concerns in infection control e.g. PPE shortage, decreasing the number of microbiological sampling to guide targeted antimicrobial treatment.

In finding a cure, many drugs have been investigated as treatment of COVID-19, some of them are antimicrobials. For example, azithromycin (in conjunction with hydroxychloroquine, an anti-malarial drug) was previously advocated in France[20], while tetracycline, doxycycline[21] and even teicoplanin[22] have also been suggested. But none of these agents is currently considered standard of therapy[23]. Of note, political factors can affect the use of antibiotics, for example, support of azithromycin by Donald Trump has caused a shortage of azithromycin in the U.S.[24]

How should antibiotics be prescribed in the context of COVID-19?

We can keep the following principles in mind when we use antimicrobials in the current pandemic[1, 25, 26]:

1. Reserve antibiotics for more severe cases
2. Select empirical antibiotics according to clinical conditions e.g. indications and risk factors for resistant bacteria
3. Review the need of antibiotics after 48-72 hours
4. Obtain microbiological sample as far as possible prior to starting treatment
5. Consider intravenous to oral switch for cases with clinical improvement, if a suitable agent is available
6. Avoid empirical use of fluoroquinolones and macrolides for risk of QT prolongation, especially when the rate of atypical pneumonia appears to be low
7. Stop antibiotics after COVID-19 status is confirmed, if no definite evidence of bacterial infection is present and clinically stable
8. Consider non-infective causes of secondary worsening relevant to COVID-19, e.g. myocarditis, cytokine release syndrome

What is the role of antibiotic stewardship (AMS) in COVID-19?

In normal times, AMS team is responsible to coordinate and implement antibiotic stewardship programme, and consists of microbiologists, infectious disease physician, infection control nurses and pharmacists[27]. Their main role is to guide clinicians to appropriately use antibiotics, such as by setting up pre-authorization mechanisms or providing immediate concurrent feedbacks to users and monitor the consumption of antibiotics and bacterial resistance patterns. In this context, AMS team is well-positioned to respond to pandemic. They possess knowledge on infectious diseases, access to laboratory and connections with pharmacists. They could identify COVID-19 patients possibly missed on admission as they review cases, communicate critical test results to clinicians directly, actively plan for the antimicrobial stocking and supply and help develop updated treatment protocol focusing on antimicrobials[28]. Some overseas authorities have already published specific antibiotic protocols for COVID-19[29-31].

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Conclusion

Amidst a highly infectious pandemic, the importance of rational use of antibiotics can be easily overlooked. While the pandemic may soon be over, the same cannot be spoken for AMR, which may in fact be exacerbated by COVID-19. Just like we need to practice our hand washing and mask wearing until a vaccine for COVID-19 is available, we need to use existing antibiotics carefully before potential game-changing novelties enter the battlefield and save the day.

Summary

1) Despite certain new antibiotics are now available in the market, their use is still limited. We need to keep prescribing antibiotics rationally as guided by antibiotic stewardship programmes.

2) Secondary bacterial pneumonia has been a well-recognized complication of influenza, but not among coronaviruses including COVID-19 according to data so far.

3) The rate of prescription of antibiotics for COVID-19 cohorts reported is remarkably high. More prudent use of antibiotics is indicated to reduce emergence of antibiotic resistance when the pandemic is over.

4) In COVID-19 pandemic, antibiotics should be reserved for more severe cases and discontinued if no definite evidence of bacterial infection in uncomplicated cases.

5) We should be cautious when using biomarkers to aid us in deciding when to start or stop antibiotics in the context of COVID-19, as their roles have not been well-defined. A similar cautious approach applies to using immunodiagnostic point-of-care tests for diagnosis.

Additional Information

Biomarkers for prediction of bacterial infection

The biomarker procalcitonin has been employed to predict bacterial infections clinically, but their utility for COVID-19 is currently uncertain. While values are low in most patients with COVID-19, they appear to rise with disease severity as part of the systemic inflammatory process regardless of secondary infections[32]. Therefore, routine testing to guide decisions on antibiotics cannot be recommended. Other biomarkers e.g. C-reactive protein (CRP) are even less predictive[29]. We should bear in mind that biomarkers are adjunctive tools. Overall clinical picture should always be considered when starting or stopping antibiotics.

Classification and limitation of rapid diagnostic test

An early diagnosis can facilitate clinical management and infection control. For a completely new infection like COVID-19, the Food and Drug Administration (FDA) would grant emergency use authorizations (EUA) to previously unapproved tests for use under specified conditions based on laboratory data, scientific literature and clinical need. At the time of writing, 68 in-vitro diagnostic tests have been granted EUA, most are laboratory-based molecular and serology tests[33]. A few of them can be used at the point of care e.g. clinics with results available in a short time frame e.g. within 1 hour, but widespread use in such setting is limited by the high cost for molecular-based tests (including film-array which is a multiplex PCR system simultaneously detecting over 20 respiratory pathogens), especially if the test volume is small, and the lower sensitivity and specificity for immunodiagnostic tests. According to World Health Organization (WHO), the latter should not be used for diagnosis of COVID-19 until more supporting evidence is available[34].

The reference list is available upon request from our secretariat at 2388 2728

Questions:

Q1 Which of the following is <u>correct</u> about the current scenario of antimicrobial resistance (AMR) worldwide?

A) 70000 deaths occur annually due to infection with resistant organisms
B) Mortality related to AMR is similar to that of COVID-19
C) Up to 1 in 10 surgical site infections in developed countries are caused by drug-resistant organisms
D) If no action is taken, 10 million per year can die due to AMR by 2050
E) If no action is taken, economic loss due to AMR can mount up to SARS in 2003

Q2 Which of the following is <u>not</u> an example of rational use of antibiotics?

A) Select empirical antibiotics according to clinical conditions as stated in guidelines
B) Review the need of antibiotics after 48-72 hours
C) Keep duration as short as possible
D) For those on parenteral antibiotics, consider switching to oral route upon clinical improvement
E) Always use the broadest spectrum of antibiotics to cover for the most resistant organisms

Q3 Bacteria that are more common to cause post-influenza pneumonia include the following <u>except</u>:

A) *Staphylococcus aureus*
B) *Streptococcus pneumoniae*
C) *Legionella pneumophila*
D) *Streptococcus pyogenes*
E) *Haemophilus influenzae*

Q4 Antibiotic Stewardship team in a pandemic can help in the following ways <u>except</u>:

A) Update clinical management protocol related to antimicrobials
B) Identify infected cases possibly missed on admission
C) Anticipate shortage of drugs and advise pharmacy to keep adequate stocks of anti-infectives
D) Communicate critical laboratory results to clinicians
E) Perform microbiological sampling on suspected and confirmed cases

Q5 Choose the <u>correct</u> statement

A) A high procalcitonin level in COVID-19 is always an indication to start empirical antibiotics
B) C-reactive protein is a highly specific marker for bacterial infections
C) Polymerase chain reaction (PCR)-based tests are generally more sensitive and specific than immunodiagnostic tests
D) Emergency use authorization (EUA) is granted by the WHO for an in-vitro diagnostic test to be used clinically under emergency situations e.g. COVID-19 pandemic
E) Most diagnostics tests on the list of EUA are point-of-care tests instead of laboratory-based tests

Answer to Self Study CME Series No. 216 (May 2020)

ANSWER: 1) C 2) E 3) D 4) D 5) E

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*Please submit your answers with the Reply Form (as insert of this Bulletin) by fax: 2385 5275 or email: hkdumail@hkdu.org