Check for updates

Received: 22 September 2021 | Accepted: 22 September 2021

DOI: 10.1111/resp.14166

COMMENTARY

Official Journal of the Asian Pacific Society of Respirology
Respirology APSR WILEY

Antibiotic-resistant bacteria: COVID-19 hasn't made the challenge go away

We are currently immersed in the problems of the COVID-19 pandemic and the whole world is now acutely aware of the threat that respiratory infections have long posed to human beings. Part of the cultural upheaval generated by COVID-19 is probably the underlying general feeling in the community that infections had largely been 'beaten' by modern antibiotic and anti-viral therapy, a phenomena many clinicians have faced when confronted with informing a family that a relatively young and previously healthy person has died of pneumonia or some other cause of sepsis.

Prior to COVID-19, the public was intermittently reminded that we were facing increasing problems with antibiotic-resistant bacteria, sometimes through reasoned documentaries but more often by more tabloid style reports of 'super bugs'. Perspectives on the threat posed by antibiotic-resistant organisms amongst clinicians understandably vary considerably depending on how common these pathogens are in their clinical practice. The development of antibiotic resistance is not always immediate or obvious. Thus, clinicians may perceive the harms of broad-spectrum antibiotics to be theoretical rather than a reality when making decisions on antimicrobial therapy in real time. When COVID-19 finally subsides and we are back to business as usual, how real a threat are antibiotic-resistant bacteria, do we really need to do anything about it and what is within the power of clinicians that can have a meaningful effect?

First, distinguishing between community-level bacterial antibiotic resistance and hospital-level resistance is important. Multiple sources of data show that community-level antibiotic resistance is related to consumption of antibiotics in the community,[1,2] especially for viral upper respiratory tract infections in children,[3,4] as well as by the use of antibiotics in raising animals.[5] Widespread availability of antibiotics without medical governance in some countries also contributes significantly to antibiotic resistance. This practice emerged as a major problem with surgical tourism prior to COVID-19,[6] particularly in the case of high-level resistance in Gram-negative bacteria such as that conferred by New Delhi metallo-beta-lactamase-1 (NDM-1).[7] The combination of poorly regulated antibiotic markets, poverty and inadequate resourcing for proper case management are also considered to be the key factors driving multidrug-resistant tuberculosis in Asia and Africa.[8] In the developing world, not only overuse of antibiotics but also failure to complete an adequate course of therapy contributes to higher rates of resistance, a noteworthy concern with tuberculosis.

Given the causes of community antibiotic resistance, the solutions lie in the community and hospital-based initiatives will have little to no impact. However, one area of concern where respiratory physicians may have a key role is ensuring the appropriate use of macrolides as chronic therapy in diseases such as bronchiectasis, chronic obstructive pulmonary disease and asthma. Worldwide, the use of azithromycin, in particular, has been associated with the rapid development of significant macrolide resistance in a host of pathogens.[9,10] While future development of non-antimicrobial macrolides that retain their immunomodulatory properties is a possibility, tight control of azithromycin use in the interim is appropriate given the resistance concerns.

In the hospital setting, entirely different factors drive emergence of antibiotic-resistant pathogens. Widespread use of broad-spectrum antibiotics across a variety of indications is the driving factor for a host of problematic pathogens including vancomycin-resistant enterococci, methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa*. The co-location of vulnerable hosts and suboptimal infection control practices further contribute to the spread of these pathogens. However, the most highly resistant organisms are generally a consequence of prolonged inpatient antibiotic therapy in increasingly elderly and comorbid patients. Prolonged antibiotic therapy perpetuates antibiotic resistance by an eradicating susceptible strains but selecting for resistance strains that subsequently multiply and become the dominant bacteria in the host. In these patients, infection with highly antibiotic-resistant pathogens is a marker of a compromised host approaching end of life where clearance of the infection is insufficient in itself to alter the overall prognosis.

A classic example of a process designed to select for highly resistant pathogens is ventilator-associated pneumonia, where pathogens such as MRSA and *P. aeruginosa* have long been endemic but, in the last few decades, carbapenem-resistant *Klebsiella* and *Acinetobacter baumannii* have become problematic in many intensive care units worldwide.[11] Pan-resistant Enterobacterales are being reported in some settings, almost exclusively in patients receiving multiple courses of antibiotics

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.
© 2021 The Authors. Respirology published by John Wiley & Sons Australia, Ltd on behalf of The Asian Pacific Society of Respirology.

for serial infections.[12,13] Different societal approaches to end-of-life management and treatment limitations to potentially futile care also significantly impact the rate of development and spread of antibiotic resistant pathogens.[14,15]

Reducing the burden of multi-antibiotic-resistant pathogens in our hospitals requires active management by all clinicians prescribing antibiotics. Broad-spectrum antibiotics should be avoided unless a significant epidemiological risk of a pathogen that would require them is present. Significant overuse of broader spectrum beta-lactam/beta-lactamase antibiotics and anti-MRSA therapy was the driving reason for the abandonment of the concept of healthcare-associated pneumonia in the recent American Thoracic Society and Infectious Diseases Society of America community-acquired pneumonia (CAP) guidelines.[16] Two key principles in the new CAP guidelines are the use of narrow-spectrum antibiotic therapy unless specific risk factors exist, and if broad-spectrum antibiotics are used, mandatory culturing of blood and respiratory secretions to both demonstrates the local presence of these pathogens as well as to enable early de-escalation if none is detected. These principles should apply to all antibiotic use in our hospitals and clinicians should always be asking 'does my patient still need antibiotics' and 'can I narrow the spectrum of antibiotic therapy I am currently giving'? Abundant evidence documents that clinicians do not do this well at present, particularly in critically ill patients; hence, antibiotic stewardship programmes are frequently required to drive a change in practice.[17]

Setting appropriate goals of care and treatment plans to avoid futile care should be considered in all patients.[14] Strong attention to infection control principles to limit the spread of resistant pathogens between patients is also critical. COVID-19 has shown how challenging good infection control can be in hospitals and hopefully this will lead to a marked shift in how we design, build, staff, manage and clean our hospitals moving forward.

Finally, while there is a lot of cause for concern about the threat of antibiotic-resistant bacteria, there is also cause for optimism. At a community level, multifaceted interventions can reduce community antibiotic consumption[18] and regulators in many countries have introduced legislation to limit the use of antibiotics in food production. In hospitals, good infection control practices and enhanced cleaning can dramatically reduce the spread of antibiotic-resistant pathogens.[19,20] Reducing the use of unnecessary broad-spectrum antibiotics does result in fewer resistant pathogens,[21–23] showing that bacteria are not innately driven to become more and more resistant but are simply responding to environmental pressures. COVID-19 has led to a massive uplift in rapid diagnostic capacity in western countries, at least for respiratory infections. More accurate diagnostics is likely to prove to be an enormous boon for antibiotic stewardship. The excellent negative predictive value of many rapid diagnostic platforms can reliably allow for antibiotic de-escalation, reducing the rate of development of nosocomial antibiotic resistance,[24–26] provided we can get clinicians to de-escalate therapy appropriately.

KEYWORDS
antibiotics, antimicrobial stewardship, bacteria, pneumonia, resistance

CONFLICT OF INTEREST

None declared.

Grant Waterer MBBS, PhD[1]
Chiagozie Ifeoma Pickens MD[2]
Richard Wunderink MD[2]

[1]*Faculty of Medicine, University of Western Australia, Royal Perth Hospital, Perth, Western Australia, Australia*
[2]*Feinberg School of Medicine, Northwestern University, Chicago, Illinois, USA*

ORCID
Grant Waterer https://orcid.org/0000-0002-7222-8018
Richard Wunderink https://orcid.org/0000-0002-8527-4195

REFERENCES

1. Baquero F, Baquero-Artigao G, Canton R, Garcia-Rey C. Antibiotic consumption and resistance selection in *Streptococcus pneumoniae*. J Antimicrob Chemother. 2002;50(Suppl S2):27–37.
2. Kahlmeter G, Menday P, Cars O. Non-hospital antimicrobial usage and resistance in community-acquired *Escherichia coli* urinary tract infection. J Antimicrob Chemother. 2003;52:1005–10.
3. Gerber JS, Jackson MA, Tamma PD, Zaoutis TE, Committee on Infectious Diseases, Pediatric Infectious Diseases Society. Antibiotic stewardship in pediatrics. Pediatrics. 2021;147:e2020040295.
4. Chung A, Perera R, Brueggemann AB, Elamin AE, Harnden A, Mayon-White R, et al. Effect of antibiotic prescribing on antibiotic resistance in individual children in primary care: prospective cohort study. BMJ. 2007;335:429.
5. Manyi-Loh C, Mamphweli S, Meyer E, Okoh A. Antibiotic use in agriculture and its consequential resistance in environmental sources: potential public health implications. Molecules. 2018;23(4):795.
6. Foley BM, Haglin JM, Tanzer JR, Eltorai AEM. Patient care without borders: a systematic review of medical and surgical tourism. J Travel Med. 2019;26:taz049.
7. Wilson ME, Chen LH. NDM-1 and the role of travel in its dissemination. Curr Infect Dis Rep. 2012;14:213–26.
8. Pradipta IS, Forsman LD, Bruchfeld J, Hak E, Alffenaar JW. Risk factors of multidrug-resistant tuberculosis: a global systematic review and meta-analysis. J Infect. 2018;77:469–78.
9. Doan T, Worden L, Hinterwirth A, Arzika AM, Maliki R, Abdou A, et al. Macrolide and nonmacrolide resistance with mass azithromycin distribution. N Engl J Med. 2020;383:1941–50.
10. Mack I, Sharland M, Berkley JA, Klein N, Malhotra-Kumar S, Bielicki J. Antimicrobial resistance following azithromycin mass drug administration: potential surveillance strategies to assess public health impact. Clin Infect Dis. 2020;70:1501–8.
11. Kalil AC, Metersky ML, Klompas M, Muscedere J, Sweeney DA, Palmer LB, et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin Infect Dis. 2016;63:e61–e111.
12. Kofteridis DP, Andrianaki AM, Maraki S, Mathioudaki A, Plataki M, Alexopoulou C, et al. Treatment pattern, prognostic factors, and outcome in patients with infection due to pan-drug-resistant gram-negative bacteria. Eur J Clin Microbiol Infect Dis. 2020;39:965–70.

13. Papadimitriou-Olivgeris M, Bartzavali C, Georgakopoulou A, Kolonitsiou F, Papamichail C, Spiliopoulou I, et al. Mortality of pandrug-resistant *Klebsiella pneumoniae* bloodstream infections in critically ill patients: a retrospective cohort of 115 episodes. Antibiotics (Basel). 2021;10:76.
14. Wilder-Smith A, Gillespie T, Taylor DR. Antimicrobial use and misuse at the end of life: a retrospective analysis of a treatment escalation/limitation plan. J R Coll Physicians Edinb. 2019;49:188–92.
15. Levin PD, Simor AE, Moses AE, Sprung CL. End-of-life treatment and bacterial antibiotic resistance: a potential association. Chest. 2010; 138:588–94.
16. Metlay JP, Waterer GW, Long AC, Anzueto A, Brozek J, Crothers K, et al. Diagnosis and treatment of adults with community-acquired pneumonia. An official clinical practice guideline of the American Thoracic Society and Infectious Diseases Society of America. Am J Respir Crit Care Med. 2019;200:e45–67.
17. Wunderink RG, Srinivasan A, Barie PS, Chastre J, Dela Cruz CS, Douglas IS, et al. Antibiotic stewardship in the intensive care unit. An official American Thoracic Society Workshop Report in collaboration with the AACN, CHEST, CDC, and SCCM. Ann Am Thorac Soc. 2020;17:531–40.
18. Cross EL, Tolfree R, Kipping R. Systematic review of public-targeted communication interventions to improve antibiotic use. J Antimicrob Chemother. 2017;72:975–87.
19. Rutala WA, Kanamori H, Gergen MF, Knelson LP, Sickbert-Bennett EE, Chen LF, et al. Enhanced disinfection leads to reduction of microbial contamination and a decrease in patient colonization and infection. Infect Control Hosp Epidemiol. 2018;39:1118–21.
20. Anderson DJ, Chen LF, Weber DJ, Moehring RW, Lewis SS, Triplett PF, et al. Enhanced terminal room disinfection and acquisition and infection caused by multidrug-resistant organisms and *Clostridium difficile* (the Benefits of Enhanced Terminal Room Disinfection study): a cluster-randomised, multicentre, crossover study. Lancet. 2017;389:805–14.
21. Yusef D, Hayajneh WA, Bani Issa A, Haddad R, Al-Azzam S, Lattyak EA, et al. Impact of an antimicrobial stewardship programme on reducing broad-spectrum antibiotic use and its effect on carbapenem-resistant *Acinetobacter baumannii* (CRAb) in hospitals in Jordan. J Antimicrob Chemother. 2021;76:516–23.
22. Garcia-Rodriguez JF, Bardan-Garcia B, Pena-Rodriguez MF, Alvarez-Diaz H, Marino-Callejo A. Meropenem antimicrobial stewardship program: clinical, economic, and antibiotic resistance impact. Eur J Clin Microbiol Infect Dis. 2019;38:161–70.
23. Peters AT, Pickens CI, Postelnick MJ, Zembower TR, Qi C, Wunderink RG. Decreasing incidence of *Acinetobacter baumannii* pneumonia and trends in antibiotic consumption: a single-center retrospective observational study. Infect Control Hosp Epidemiol. 2021. doi:10.1017/ice.2021.348
24. Paonessa JR, Shah RD, Pickens CI, Lizza BD, Donnelly HK, Malczynski M, et al. Rapid detection of methicillin-resistant *Staphylococcus aureus* in BAL: a pilot randomized controlled trial. Chest. 2019;155:999–1007.
25. Pickens CI, Qi C, Postelnick M, Paonessa J, Donnelly HK, Wunderink RG. Association between a rapid diagnostic test to detect methicillin-resistant *Staphylococcus aureus* pneumonia and decreased vancomycin use in a medical intensive care unit over a 30-month period. Infect Control Hosp Epidemiol. 2021. doi:10.1017/ice.2020.1406
26. Pickens CO, Gao CA, Cuttica MJ, Smith SB, Pesce LL, Grant RA, et al. Bacterial superinfection pneumonia in patients mechanically ventilated for COVID-19 pneumonia. Am J Respir Crit Care Med. 2021. doi:10.1164/rccm.202106-1354OC

How to cite this article: Waterer G, Pickens CI, Wunderink R. Antibiotic-resistant bacteria: COVID-19 hasn't made the challenge go away. Respirology. 2021;26:1024–6. https://doi.org/10.1111/resp.14166