EDITORIAL COMMENTARY

Antimicrobial Stewardship in a Pandemic: Picking Up the Pieces

Daisuke Furukawa[1] and Christopher J. Graber[1,2]

[1]Division of Infectious Diseases, David Geffen School of Medicine, University of California, Los Angeles, California, USA, and [2]Infectious Diseases Section, VA Greater Los Angeles Healthcare System, Los Angeles, California, USA

Coincident with the onset of the coronavirus disease 2019 (COVID-19) pandemic, studies have demonstrated higher rates of inpatient utilization of overall, broad-spectrum, and narrow-spectrum antibiotics [1, 2]. In this issue of *Clinical Infectious Diseases*, Vaughn and colleagues reviewed antibiotic utilization and rates of bacterial coinfection for patients hospitalized with COVID-19 at 38 hospitals in Michigan that were enrolled in a statewide multi-institutional collaborative quality initiative specifically aimed at improving care for patients hospitalized with COVID-19 [3]. Of 1705 reviewed patients admitted with COVID-19, 56.6% received empiric antibiotic therapy, despite only 3.5% having a documented community-onset bacterial coinfection. Although this large discordance between rates of antibiotic use and bacterial coinfection with COVID-19 has been described in the literature [4, 5], this study adds further validation to the existing body of evidence given its large multicenter study design and its detailed analysis of descriptive data on initial patient characteristics, empiric antibiotic choice and duration, and type of infection early in the hospitalization, as well as risk factors for empiric antibiotic use and community-acquired bacterial coinfection.

The authors conclude that "given the potential harms to patients and society from unnecessary antibacterial use . . . it is imperative that we develop strategies to help clinicians prescribe antibacterials judiciously to hospitalized patients with COVID-19." So, what should these strategies be? Strategies that antimicrobial stewardship programs (ASPs) can devise are best conceptualized according to phases of inpatient management of COVID-19 disease:

1. Initial management (first 48 hours of hospitalization), with an ASP focus on diagnostics and speed in relaying their findings, balanced by concerns regarding aerosolizing procedures;
2. 48–96 hours into hospitalization, with an ASP focus on discontinuation or deescalation of antimicrobial therapy if bacterial infection is unlikely;
3. Beyond 96 hours from admission, with an ASP focus on enforcing proper treatment duration (if bacterial coinfection is indeed present).

INITIAL MANAGEMENT

Vaughn et al highlight the impact of rapid and timely COVID-19 diagnosis on antibiotic use. They found that patients who did not receive empiric antibiotics were more likely to have had a COVID-19 polymerase chain reaction (PCR) test result in <1 day compared to those who did receive empiric antibiotics (64.9% vs 76.4%). Additionally, the proportion of patients receiving empiric antibiotic therapy decreased over time as proportion of tests resulting in <1 day increased with increased testing capacity. Decrease in antibiotic prescription with use of rapid viral testing has been demonstrated with influenza [6], and this study suggests that a similar pattern is observed with patients with COVID-19. ASPs should therefore focus their efforts on increasing testing capacity so that providers can rapidly identify patients with COVID-19 and potentially prevent unnecessary antibiotic prescription. This rapid identification can also be coupled with timely communication and decision support by ASP. In cases of bacteremia, rapid diagnostics are most effective when coupled with decision support from ASP [7], and although interpretation of COVID-19 tests is in no way as complex as the multiplex PCR panels used for bacteremia, there is still likely a role for ASPs to help providers ascertain risk factors for bacterial coinfections and need for antibiotics in the setting of a positive COVID-19 test, particularly in patients presenting with mild to moderate disease.

Respiratory culture is another point of ASP focus during the first phase of

management. However, obtaining respiratory cultures must be done while balancing the risk of aerosolization from performing diagnostic procedures like bronchoalveolar lavage or induced sputum. The authors noted that only 7.7% of patients had respiratory cultures obtained and speculated that fear of aerosolization may have contributed to the low rate. Given this, ASPs can additionally engage in diagnostic stewardship to optimize utility of respiratory cultures. In keeping with 2019 community-acquired pneumonia treatment guideline, even for patients presenting with confirmed COVID-19, those who are most likely to benefit from cultures are likely those presenting with severe disease or those empirically treated with broad-spectrum antibiotics [8, 9]. Disease severity was identified as a risk factor for bacterial coinfection in this study, which further supports the idea that respiratory culture should be prioritized for those presenting with severe disease.

48–96 HOURS INTO HOSPITALIZATION

Although Vaughn et al note that the most common empiric antibiotics prescribed were antibiotics with community-acquired coverage, 12.5% of patients were given anti-methicillin-resistant *Staphylococcus aureus* (MRSA) antibiotics, and 14.9% were given anti-pseudomonal antibiotics. Although the study did not evaluate appropriateness of these broad-spectrum agents, this finding suggests that there is a role for ASPs to help deescalate antibiotics 48–96 hours into the hospitalization based on assessment of risk factors and culture data. This again speaks to the importance of obtaining initial cultures as described above. In cases of bacterial pneumonia, studies have demonstrated clinical benefits and safety with deescalation of antibiotics [10–12]. The same principle should apply for patients with COVD-19 and bacterial coinfection.

One unique difference between patients with bacterial community-acquired pneumonia and patients with COVID-19 is that depending on diagnostic data, stopping antibiotics completely after 48–96 hours may be appropriate. Vaughn et al showed that 54.4% of patients started on empiric antibiotics had their antibiotics discontinued within 1 day after COVID-19 testing returned positive. Furthermore, 35.9% of patients who were continued on antibiotics and did not have confirmed community-onset bacterial coinfection had antibiotics discontinued within 5 days, a duration shorter than what is recommended for treatment of bacterial pneumonia. Although the study did not provide any outcome data as it pertains to duration of antibiotics, the data suggest that early discontinuation of antibiotics is feasible and likely appropriate for patients with COVID-19, particularly considering the low rates of bacterial coinfection observed in this study.

BEYOND 96 HOURS

The authors also found that 24.5% of patients without bacterial coinfection received antibiotics for >7 days, a duration longer than what is typically recommended even for hospital-acquired or ventilator-associated pneumonia. The study did not include clinical data beyond the first 2 days of hospitalization; thus, it is unclear if clinical circumstance were present that may have justified the prolonged antibiotic course. Regardless, even prior to the pandemic, excessive treatment duration for pneumonia has been identified as a stewardship target [13–15], and the same stewardship efforts should be continued for patients with COVID-19 with concurrent bacterial coinfection.

ASP responsibility does not end with completion of the initial course of antibiotics prescribed to patients. Often patients with COVID-19 experience prolonged hospital courses, with many days on the ventilator, increasing the risk of hospital-acquired infections. ASPs should continue to be involved with the clinical care of patients and assist providers in differentiating colonization from true infection, assessing need for antibiotic therapy, and prescribing the most optimal antibiotics at the right dose, route, and duration.

Vaughn et al bring attention to an important and unfortunate by-product of the COVID-19 pandemic: indiscriminate prescribing of antibiotics for patients hospitalized with COVID-19. For this, the pandemic has brought a new and unique demand for antimicrobial stewardship. However, this demand comes at a time when stewards are in need of more dedicated time and resources to support their ASP efforts, as many have played a key role in their facilities' pandemic response, spending countless hours on COVID-19-specific policies and guidelines at the expense of usual ASP activities. As the COVID-19 pandemic continues to evolve, an important challenge to address will be how best to support the resumption of ASPs so that they can "pick up the pieces" in limiting indiscriminate antimicrobial use.

Note

References

1. Nestler M, Godbout E, Lee K, et al. Impact of COVID-19 on pneumonia-focused antibiotic use at an academic medical center. Infect Control Hosp Epidemiol **2020**:1–9. doi:10.1017/ice.2020.362
2. Abelenda-Alonso G, Padulles A, Rombauts A, et al. Antibiotic prescription during the COVID-19 pandemic: a biphasic pattern. Infect Control Hosp Epidemiol **2020**:1–8. doi:10.1017/ice.2020.381
3. Vaughn V, Gandhi T, Petty LA, et al. Empiric antibacterial therapy and community-onset bacterial coinfection in patients hospitalized with COVID-19: a multi-hospital cohort study. Clin Infect Dis **2020**:5895253. doi:10.1093/cid/ciaa1239
4. Rawson TM, Moore LSP, Zhu N, et al. Bacterial and fungal coinfection in individuals with coronavirus: a rapid review to support COVID-19 antimicrobial prescribing. Clin Infect Dis **2020**:ciaa530. doi:10.1093/cid/ciaa530.
5. Clancy CJ, Nguyen MH. COVID-19, superinfections and antimicrobial development: what can we expect? Clin Infect Dis **2020**:ciaa524. doi:10.1093/cid/ciaa524. Online ahead of print.
6. Egilmezer E, Walker GJ, Bakthavathsalam P, et al. Systematic review of the impact of point-of-care testing for influenza on the outcomes of patients

with acute respiratory tract infection. Rev Med Virol **2018**; 28:e1995.

7. Barlam TF, Cosgrove SE, Abbo LM, et al. Implementing an antibiotic stewardship program: guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. Clin Infect Dis **2016**; 62:e51–77. doi:10.1093/cid/ciw118.

8. Metlay JP, Waterer GW, Long AC, 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.

9. Metlay JP, Waterer GW. Treatment of community-acquired pneumonia during the coronavirus disease 2019 (COVID-19) pandemic. Ann Intern Med **2020**; 173:304–5. doi:10.7326/M20-2189.

10. Cowley MC, Ritchie DJ, Hampton N, Kollef MH, Micek ST. Outcomes associated with de-escalating therapy for methicillin-resistant *Staphylococcus aureus* in culture-negative nosocomial pneumonia. Chest **2019**; 155:53–9.

11. Yamana H, Matsui H, Tagami T, Hirashima J, Fushimi K, Yasunaga H. De-escalation versus continuation of empirical antimicrobial therapy in community-acquired pneumonia. J Infect **2016**; 73:314–25.

12. Viasus D, Simonetti AF, Garcia-Vidal C, Niubó J, Dorca J, Carratalà J. Impact of antibiotic de-escalation on clinical outcomes in community-acquired pneumococcal pneumonia. J Antimicrob Chemother **2017**; 72:547–53.

13. Foolad F, Huang AM, Nguyen CT, et al. A multicentre stewardship initiative to decrease excessive duration of antibiotic therapy for the treatment of community-acquired pneumonia. J Antimicrob Chemother. **2018**; 73:1402–7. doi:10.1093/jac/dky021.

14. Madaras-Kelly KJ, Burk M, Caplinger C, et al; Pneumonia Duration of Therapy Medication Utilization Evaluation Group. Total duration of antimicrobial therapy in veterans hospitalized with uncomplicated pneumonia: results of a national medication utilization evaluation. J Hosp Med **2016**; 11:832–9.

15. Yi SH, Hatfield KM, Baggs J, et al. Duration of antibiotic use among adults with uncomplicated community-acquired pneumonia requiring hospitalization in the United States. Clin Infect Dis **2018**; 66:1333–41. doi:10.1093/cid/cix986.