Has the Antibiotic Course Had Its Day?

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Abstract

Therapeutic interventions for infectious diseases are complicated by multiple factors, including unknowns surrounding the identity of the infectious agent(s), the bacterial load, and the organism's susceptibility to different antibiotics or antibiotic classes. Unknown host factors also include pharmacokinetic considerations (absorption, distribution, metabolism, etc.) that influence the efficacy of even the best therapeutic options. Given the lack of information available with which to initiate treatment, clinicians must make decisions (e.g., drug/drug class, dosing, treatment durations, etc.) based on incomplete information, which typically leads to the implementation of defined treatment guidelines and protocols.

Recently, Llewelyn et al. published an article in *The BMJ* questioning current principles in antibiotic stewardship and suggesting the current "complete the course" policy is invalid. This note does not disagree with the claims of Llewelyn et al., but rather, uses that study as inspiration to expand upon the discussion and provide additional insight into the history, challenges, and potential solutions for antibiotic therapies. As with many healthcare challenges, such solutions will likely rely on continued technological advancement and investments in precision medicine diagnostics.

Main Article

Much fanfare was made during the summer of 2017 about an article published in *The BMJ* entitled "The Antibiotic Course Has Had Its Day" (Llewelyn et al., 2017). Despite the article's provocative title, it raises an important issue regarding antibiotic dose and treatment durations that has perplexed researchers, healthcare professionals, and regulators since Alexander Fleming and Howard Florey began characterizing penicillin in the 1920s and 1930s (Aminov, 2010; Chain et al., 1940; Fleming, 1929). While the mission of the Llewelyn et al. manuscript was to promote an understanding of antibiotic use and misuse among healthcare professionals and the public, the content of the article was somewhat overshadowed by its bold, conclusive title, to which the media focused their attention. That is not to say the antibiotic course has not had its day, but to conclude so based on the (somewhat) limited data presented in the manuscript was reckless. What is obvious from reading the comments on the manuscript on social media, and speaking with practitioners, is that healthcare professionals do not dispute that current antibiotic policies may be suboptimal. However, what the article promotes is an erosion of confidence between patients and medical professionals, without putting forward any potential—or substantive—solutions to the problem.

How did we get here?

The idea that undertreating infections with insufficient antibiotic causes resistance came about shortly following the discovery of penicillin. Early *in vivo* studies revealed that patients or mice that received low doses of penicillin succumbed to streptococcal infections, regardless of treatment duration. In addition, patients receiving elevated doses of penicillin—and who appeared to have recovered from infections—subsequently deteriorated and succumbed to

infection following the cessation of treatment (Abraham et al., 1941; Chain et al., 1940; Heatley, 1970). Such observations could have been caused by multiple factors, but is was largely assumed that the infectious agent developed resistance due to low-dose treatments, or that the treatments were not sufficiently long to reduce the bacterial load to non-life-threatening levels. Thus, over time, such observations led to the generally-accepted approach that infections should be treated early with high doses (i.e., hit hard and hit fast; (Ehrlich, 1913)), and that treatments should be prolonged to ensure the infectious agent has been cleared from the host (Pena-Miller et al., 2013).

A Complex Balance Exists Between Dose And Time

While the benefits of early antibiotic administration are rarely (if ever) disputed, there are contrasting data to support the appropriate doses and treatment durations. All bacteria exposed to drugs will develop resistance to that agent over time and the likelihood of that occurring increases with increasing treatment durations (Francino, 2015). Thus, a complex balance exists between dose and time. Too short a treatment and bacterial loads are not cleared or sufficiently reduced, while too long a treatment may be detrimental due to the promotion, selection, and colonization of antibiotic-resistant bacteria, which can then cause recurrent episodes of infection (Ventola, 2015). Thus, reduced doses and treatment durations may also reduce resistance by not prolonging selective pressures (Michael, Dominey-Howes, & Labbate, 2014). In fact, multiple studies showed that the rates of relapse are not higher in patients who complete full courses of antibiotic treatment versus those that cease treatment once symptoms diminish (Agarwal et al., 2004; Tellier, Niederman, Nusrat, Patel, & Lavin, 2004). However, the challenge then becomes determining when symptoms have improved sufficiently to justify treatment cessation—and who makes the decision; the patient/guardian or a qualified medical practitioner?

Antibiotic resistance occurs through multiple avenues, including selection for beneficial mutations, the acquisition of resistance genes from the environment or other bacteria (e.g., horizontal gene transfer), or adaptation (e.g., increased efflux-pump activity or increased production of antibiotic targets) (Blair, Webber, Baylay, Ogbolu, & Piddock, 2015). Llewelyn et al. distinguish between “target selection” and “collateral selection” (Box 1 in Llewelyn et al., 2017), and suggest that most species threatening humankind do not develop resistance through target selection. The rationale for this suggestion was somewhat murky and the authors suggest that since the ESKAPE pathogens (with *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumanii*, *Pseudomonas aeruginosa,* and *Enterobacter* spp.) are human commensals and opportunistic pathogens that collateral selection predominates. However, as an example, it should be noted that multiple ESKAPE-pathogen-associated infections are treated using ?-lactam/?-lactamase inhibitor combinations, to which resistance is acquired through the selection of mutations in the ?-lactamase target (Drawz & Bonomo, 2010).

Antibiotics also negatively affect the host in multiple ways, which should be a primary consideration when evaluating antibiotic courses. Many antibiotics are toxic to eukaryotic cells and as expected, the ensuing damage increases with prolonged exposure times (Kahlmeter & Dahlager, 1984). In addition, antibiotics play a substantial role in the clearance of healthy or commensal bacteria, and in the development/selection of resistance in such strains (Langdon, Crook, & Dantas, 2016). Indeed, the effects of antibiotics on the microbiome are many, including metabolic, immunological, and developmental disorders—not to mention that dysbiosis in the microbiome also affects one’s ability to subsequently resist infection (Cuthbertson et al., 2016; Holmes et al., 2008; Hsiao et al., 2013; Lewis et al., 2015; Marchesi et al., 2007; Smith et al., 2013; Stefka et al., 2014; Teo et al., 2015). Such factors become particularly concerning for infants and children whose microbiomes are developing in predictable succession, the disruption of which can be pathogenic and hold lifelong consequences (Holmes et al., 2008; Marchesi et al., 2007; Smith et al., 2013; Stefka et al., 2014).

One final complicating factor regarding antibiotic dosing and treatment durations that will be mentioned here is that of concentration- (fluoroquinolones, aminoglycosides) and time-dependent (?-lactams, glycopeptides, oxazolidinones)

antibiotics (Pea & Viale, 2009). Concentration-dependent antibiotics fall into the “hit hard, and hit fast” camp, where high doses for less time may yield better results than lower doses for longer durations. For example, in a clinical trial of hospitalized patients with community-acquired pneumonia, once-daily treatment of 750 mg levofloxacin for 5 days had the same clinical success to once-daily treatment of 500 mg levofloxacin for 10 days (Pea & Viale, 2009; Shorr, Khashab, Xiang, Tennenberg, & Kahn, 2006). However, the shorter time-course approach resolved purulent sputum and fever better than that of the longer/lower dose approach, suggesting that for dose-dependent antibiotics, shorter time courses are beneficial. A similar finding was also observed from a meta-analysis of 21 randomized trials of patients with bacterial infections where a once-daily dose of aminoglycosides was equal to multiple daily doses, but had a lower risk of nephrotoxicity (Barza, Ioannidis, Cappelleri, & Lau, 1996; Pea & Viale, 2009).

Conversely, the aim with time-dependent antibiotics is to access and inhibit the target for prolonged periods of time. The importance of this strategy relies on maintaining supra-inhibitory concentrations of antibiotic throughout treatment since bacterial regrowth can occur once doses fall below the minimum inhibitory concentration (Pea & Viale, 2009). An additional consideration with time-dependent antibiotics is that pertaining to the plasma levels of drugs, which is affected by multiple pharmacokinetic factors that vary widely between patients. Thus, to maintain sufficient plasma concentrations of drugs, multiple-daily-dose or infusion strategies are often required.

What can be done moving forward?

The era of precision medicine is upon us and will surely revolutionize the way infectious diseases are diagnosed and treated. Rapid diagnostics, real-time infection monitoring, knowledge of the associations between patients’ genetics and their responses to medications, and other technological advances are occurring more rapidly now than ever before, and promise to alter the way infectious diseases are viewed, addressed, and controlled in the future. One such approach to personalizing therapies for infectious diseases is that of host-directed therapies (HDT). HDTs seek to bolster microbial killing and mitigate host inflammation and damage by targeting specific regulatory host factors and pathways involved in pathogenesis (Mahon & Hafner, 2017). Multiple candidate HDT drugs have been identified (Wallis & Hafner, 2015) and now form the basis for additional studies aimed at developing drugs that target the specific host factors/pathways disrupted by pathogens (Mahon & Hafner, 2017).

The implementation of rapid diagnostic tests will also revolutionize the way infectious diseases are treated in the clinic. At their core, clinical microbiology laboratories seek to determine whether a patient is infected, and if so, with what, and what drugs can be used to treat the infectious agent? (Messacar, Parker, Todd, & Dominguez, 2017). Multiple technologies, including PCR-coupled ESI-TOF, next generation sequencing, biosensors, biomarkers, multiplexed single-step molecular cartridge-based tests, etc. promise to answer such questions rapidly (ideally in <60 minutes), and will bolster the capabilities of clinicians to implement specific and tailored therapies, rather than empiric antimicrobial therapies, which are often required and contribute to reducing the already small pool of available antibiotics (Caliendo et al., 2013).

The rapid advance of antibiotic resistance has also necessitated a shift from monotherapies to combination therapies. This is particularly true for the ESKAPE pathogens, which cause the majority of infections and are notoriously resistant to most common antibiotics (Gill, Franco, & Hancock, 2015; Lamers & Burrows, 2016; Wright, 2012). Thus, combination therapies are common since they exhibit potencies that are well beyond those of each drug independently. The conventional thought has also been that resistance to combination therapies is less likely to arise since multiple pathways, enzymes, or other factors are targeted simultaneously. Therefore, multiple avenues leading to resistance would have to occur to support survival and outgrowth. However, *in vitro* evolutionary studies and mathematical modeling found that bacteria treated with the most potent combination therapy resulted in the highest resistance, and by 5 days’ treatment, inhibited growth only marginally—whereas the control assays in which drugs were added individually continued to inhibit growth beyond day 5 (Pena-Miller et al., 2013). Notably, however, such studies were performed *in vitro* and the presence of *in vivo* host defense factors would undoubtedly affect the performance of combination therapies.

Conclusions and Future Considerations

It is likely that most healthcare professionals would agree that the current antibiotic courses are less than ideal and that there is much room for advancement. However, rather than professing that the antibiotic course has had its day, perhaps the message of Llewelyn et al. should have been one calling for more relevant and focused studies that assess the minimum antibiotic courses required for common diseases or drug classes—or promoting advances in precision medicine and diagnostics. Such suggestions are smuggled sporadically throughout the manuscript; however, the overarching conclusion was detailed in the title. For example, as the authors point out, current international guidelines recommend 10–14 days of ?-lactam treatment for pyelonephritis (of which there are >460,000 cases per year in the United States (Johnson & Russo, 2018)); however, no data exist for shorter time courses. The authors also note that in some studies, shorter treatment courses were associated with poorer patient outcomes. Indeed, it will not be possible to generalize the merits of shorter versus longer treatment durations, and it is also unlikely that such generalizations will be possible across complete antibiotic classes. This is because assessments based on antibiotic class still ignore patient factors, including prior treatment history, metabolism, and individualized pharmaco-kinetic and -dynamic concerns. Moreover, most pharmacokinetic studies aimed at defining dosing are performed using healthy individuals, not patients, and therefore, it is to be expected that differences will arise when put into practice (Pea & Viale, 2009). What seems more likely is that with methodological and technological advances, individualized care will become commonplace—and once healthcare practitioners are equipped to assess and respond to patients in such a personalized manner, then the antibiotic course will have had its day.

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