The Role of Durations on Antibiotic Resistance

Madeleine Kleven, August 23, 2019

Introduction

Antibiotics are one of the greatest health interventions of the twentieth century. They allow for the effective treatment of hundreds of pathogens that infect both humans and animals. Unfortunately, their inappropriate use has led to a dramatic increase in the number of antibiotic resistant organisms throughout the world making treatment difficult and at times even impossible. The emergence of these antibiotic resistant superbugs is highly correlated with selective pressure that results from the overuse of antibiotics.[11]

Selective pressure is the influence exerted by some environmental factor on the ability of a group of organisms to survive and reproduce. In this case, antibiotics are that factor. Bacterial organisms become resistant to antibiotics when antibiotics exert selective pressure by eliminating susceptible bacteria, allowing antibiotic-resistant bacteria to survive and proliferate, leading to a gradual increase in the proportion of bacteria that are resistant.[31] In short, the more an antibiotic is used the more bacteria resistant to that antibiotic will dominate. When this happens, doctors and veterinarians switch to other antibiotics and the process repeats so that over time bacteria become resistant to more and more drugs. We are now at the point where for some infections there are no drugs left and for many more there are only a few.

One aspect of the selection pressure along with dosage and number of patients either human, animal, or plant receiving an antibiotic is duration of use. Most simply the more an antibiotic is used either by increasing the number of patients exposed or increasing the duration of exposure, the greater the possibility the antibiotic will have to select for resistant bacteria. In patients not receiving the antibiotic or after the antibiotic has been withdrawn selection pressure maintaining or increasing the proportion of bacteria that are resistant is reduced. There is ample scientific evidence that the duration of antimicrobial use as well as dosage has an impact on the development of antibiotic resistant organisms. Optimizing the duration of treatment to reduce the risk of resistance development while still getting the benefit of the drug treatment has proven to be a challenge. However, recent evidence suggests that shorter courses of antibiotic therapy are more effective at reducing the development and spread of resistance when compared with longer durations of use. As infectious disease specialist Dr. Spellberg recently argued “shorter is better” is the “new antibiotic mantra.”[27]

Duration Reduction Studies

The development of antibiotic resistance has been frequently studied in hospital and community settings where resistance poses a great threat to human health. In these studies, researchers have found that not only can infections be successfully cleared with a reduced course of antibiotic treatment, but the development of resistance can be significantly decreased.

In a retrospective cohort study analyzing the effect of antibiotic use duration on new resistance development, Teshome et al. found that after three days of treatment, each additional day of exposure to cefepime, meropenem, and piperacillin-tazobactam was associated with an increased risk of new resistance development.[1] Chastre and colleagues identified critically ill patients with ventilator associated pneumonia (VAP) who developed recurrent infections, and found that multi-resistant pathogens emerged less frequently in those who had received a shorter length of treatment (8 days of antibiotics vs 15).[3] Additional clinical trials have found that 7– 8 days of antibiotic treatment is a sufficient duration of use for most non-bacteremic patients with ventilator-associated pneumonia.[25, 3] This is true for patients with community acquired pneumonia (CAP) as well.[26]

Researchers at the University of Michigan in collaboration with the Centers for Disease Control and Prevention recently conducted a retrospective cohort study examining outcomes associated with excess duration of antibiotic treatment in patients with pneumonia. The results were startling. They discovered that two thirds (67.8% [4391 of 6481]) of patients received antibiotic therapy exceeding the shortest effective duration, with 71.8% of community acquired pneumonia and 56.5% of health care associated pneumonia patients receiving excess treatment. This excessive treatment was associated with patient-reported adverse events.[29] In an editorial following the publication of this study, physicians Brad Spellberg and Louis Rice stated, “The cumulative evidence indicates that each day of antibiotic therapy beyond the first confers a decreasing additional benefit to clinical cure while increasing the burden of harm in the form of adverse effects, superinfections, and selection of antibiotic resistance. It is time for regulatory agencies, payers, and professional societies to align themselves with the overwhelming data and assist in converting practice patterns to short-course therapy.”[30]

In children with respiratory tract infections, post-treatment resistant pneumococcal carriage is a serious risk associated with antibiotic treatment. To determine whether short-course, high-dose amoxicillin therapy reduces risk of carriage, researchers performed a randomized trial studying children aged 6 to 59 months receiving antibiotics for respiratory illness. Patients were randomly assigned to receive 1 of 2 twice-daily regimens of amoxicillin: 90 mg/kg per day for 5 days (n = 398) or 40 mg/kg per day for 10 days (n = 397). At the conclusion of the study, researchers found the risk of penicillin-nonsusceptible pneumococcal carriage was significantly lower in the short-course, high-dose group (24%) compared with the longer 10-day course group (32%). In addition, the short-course treatment was associated with a decreased risk of trimethoprim-sulfamethoxazole non-susceptibility.[15] Researchers did not determine or record the confounding effect of dosage on the risk of antibiotic non-susceptibility compared to duration. Therefore, it is unclear whether or not altering duration alone while keeping a controlled dosage would have had the same effect on risk of antibiotic resistance development. However, it is worth noting that duration along with dosage are critical factors that must be considered when administering antibiotics.

In a similar study by Guillemot et al. scientists analyzed the risk factors for carriage of penicillin-resistant *Streptococcus pneumoniae* with a low dosage and long treatment duration of beta-lactam antibiotics. They found children who were treated with a low daily dose of an oral beta-lactam antibiotic (defined as lower than clinical recommendations) had an increased risk of carrying resistant bacteria as compared with children who did not (OR, 5.9; 95% CI, 2.1-16.7; P=.002). Length of treatment was associated with carriage as well. Treatment with an antibiotic for more than 5 days was associated with an increased risk of resistant bacteria carriage (OR, 3.5; 95% CI, 1.3-9.8; P=.02).[17]

Reduction Interventions

In several studies, hospitals and healthcare facilities implemented interventions which aimed to reduce the course of antimicrobial therapies (restricting access and limiting indications). [5] These interventions were effective in lowering antimicrobial resistance and incidence of superinfections and in many instances antimicrobial therapy costs as well.[2, 4, 6] In a review evaluating shorter courses of antibiotic therapy for nosocomial pneumonia, Dugan et al found antimicrobial therapy may be discontinued after as few as 3 days in the intensive care unit (ICU) and may decrease not only patient hospital stay, but antimicrobial resistance.[8] Physicians in a medical-surgical intensive care unit conducted an intervention to limit the duration of all antimicrobial therapies that were being prescribed for more than 14 days. In the intervention phase, 89.8% (415/462) of the prescribed antibiotics in the ICU were discontinued before day 14 and antimicrobial utilization as well as resistance rates in selected organisms were recorded and compared to the previous 10-month period. The intervention phase resulted in significant reductions in antimicrobial use and resistance compared to the previous period, with Imipenem resistance decreasing in *Acinetobacter baumannii* from 88.5% to 20.0% and in *Klebsiella pneumoniae* from 54.5% to 10.7%.[4]

In the ICU, inappropriate antibiotic use for pulmonary infiltrates is common, leading to a higher risk of antimicrobial resistance development. Researchers Singh et al. compared treatment durations in ICU patients with a low likelihood of pneumonia (clinical pulmonary infection score (CPIS) of </=6) and observed the effect of duration on antibiotic resistance and the emergence of superinfections .[2] Patients were randomized to receive one of two therapies: 1) standard therapy with choice and duration of antibiotics at the discretion of physicians or 2) experimental therapy, ciprofloxacin monotherapy with reevaluation at 3 days (ciprofloxacin was discontinued in patients at 3 days if CPIS stayed at </=6). In patients that remained stable with a CPIS of </= 6 at the evaluation point on day 3, antibiotics were still continued in 96% of patients in the standard therapy group compared to 0% of the patients in the experimental group. At the conclusion of the study researchers found that antimicrobial resistance and/or development of superinfections occurred in only 15% of patients in the experimental therapy group who received a shorter course of treatment and were taken off therapy when symptoms remained stable, compared to 35% of patients in the standard treatment group.

Models

D'Agata et al. developed a statistical modeling system to identify the key parameters contributing to the spread of antimicrobial-resistant bacteria in a hospital setting. They created an individual-based model (IBM) and a deterministic model (DEM), formulated to describe the complexities of the transmission dynamics of antibiotic-resistant bacteria. The IBM was formulated based on individual behavior and observable events, and the corresponding DEM was developed to interpret the IBM. Through the integration of these two model systems, researchers created a quantitative analysis of the emergence and spread of antibiotic-resistant bacteria and concluded that early initiation of treatment and minimization of its duration mitigate antibiotic resistance epidemics in hospitals.[12]

In an article published in the journal of infectious diseases, researchers studied the impact of duration of therapy on the emergence of *Staphylococcus aureus* resistance to a quinolone antimicrobial. Using an in-vitro model of *Staphylococcus aureus* infection, researchers examined the effect of therapy intensity and therapy duration on resistance emergence. They found duration of therapy had a significant impact on the antimicrobial's ability to suppress the resistant microorganism subpopulation. As the duration of treatment increased beyond 5 days, the intensity needed to suppress the antibiotic-resistant subpopulations increased. Tam et al. came to the conclusion that duration of therapy increases the likelihood of amplification of the resistant subpopulation. Even with reasonably intensive therapy, with enough time, isolates can have enough rounds of replication to pick up a resistance mechanism that will allow amplification of a resistant subpopulation.[7]

Effectiveness of Shortened Durations

A number of publications including meta-analyses, guidelines, and systematic reviews have confirmed that the shortening of antibiotic therapy is a safe practice which should be more consistently implemented in medical settings.[5] For a variety of illnesses from urinary tract infections to endocarditis researchers have discovered shorter durations of antibiotic therapy are equally effective in clearing infection.[10] One of the most commonly treated bacterial infections of children in the United States is acute otitis media.[22] This bacterial infection is treated with amoxicillin sometimes for 10 days. However, various researchers have found a 3-day regimen of antibiotics is just as effective.[18, 19, 20] This is the case with acute sinusitis as well. With a shortened course of therapy, selection for resistance is decreased and patients are successfully cleared of infection.[21] More physicians have altered their subscribing habits and discovered several classes of antibiotics may be given for as few as 5 days for treatment of certain respiratory tract infections.[14] Shorter course treatment regimens for several diseases including pyelonephritis, intra-abdominal infection, COPD, sinusitis, and cellulitis are just as effective as longer courses of treatment, and are safer alternatives for patients. Shorter courses of therapeutic intervention are able to reduce selective pressure driving resistance and lower the risk of developing serious infections with superbugs.[9, 27] Antibiotic treatment duration for certain community- and hospital-acquired infections can be decreased substantially and still maintain positive patient outcomes.[12,13]

Animal Studies

Two classes of antibiotics, lincosamides and macrolides, are often used to treat various common gastrointestinal and respiratory infections in cattle and pigs. However, acquired resistance to these antibiotics by organisms such as *Brachyspira* is threatening food producing animals throughout the world. In an effort to identify resistant zoonotic pathogens and analyze resistance mechanisms in these antimicrobials, Pyörälä et al. did a thorough review of their use throughout the European Union. They found that the use of these antibiotics in long-acting injections as well as in-feed result in low concentrations of the active substance in the animal for long periods of time and may contribute to the development of antimicrobial resistance.[24]

In a study by Ladely et al. scientists evaluated resistance in the bacterial foodborne pathogen *Campylobacter* in broilers given high dose treatment concentrations or low dose growth promoting concentrations of the antibiotic tylosin for different durations. When the broilers were two weeks of age they were exposed to *Campylobacter* and administered tylosin either at a low dose in feed for 4 weeks, or at a high dose in drinking water for 5 days. Overall, antibiotics resistance was observed at a significantly higher rate in *Campylobacter*, when tylosin was administered for 4 weeks (62.7%) versus 5 days (11.4%).[23]

Implications for Animals

Antibiotics are natural and synthetic compounds which through a variety of mechanistic pathways interact with bacterial targets and destroy them or slow growth by inhibiting reproduction. Although dosage along with other host specific differences may alter host response, the antibiotic mechanism remains constant in both animals and humans. Humans and animals use many of the same antibiotic classes and are affected by many of the same pathogens. Resistance in these pathogens harms both animal and human health.

The use of any class of antimicrobial agent will inevitably lead to a selection pressure in favor of resistant subpopulations. This selection pressure is heavily influenced by antimicrobial characteristics as well as the dose, treatment interval and duration of treatment. Consistent with this, the emergence of bacterial resistance can be minimized by decreasing the length of time that drug levels are present in the infected tissue.[28] In a medical and laboratory setting, reducing antibiotic use duration is an effective method in reducing the risk of antibiotic resistance development. Though, further research must be conducted in animal medicine, the available evidence suggests that there is a lower risk of resistance development when duration limits are decreased and it is likely that animal hosts may see similar levels of antibiotic effectiveness with shorter durations.

As antibiotic resistance continues to develop and spread across the world, efforts to minimize antimicrobial use must be prioritized in both an agricultural and medicinal setting. If we are to preserve the effectiveness of antibiotics and minimize the public health hazard that AMR poses, antibiotics must be used more judiciously in agriculture. This must include limiting antibiotic use to sick animals and shortening the duration of antibiotic use when the drugs are needed.

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