In the Literature

A Randomized Trial of Antibiotic Streamlining in Community-Acquired Pneumonia (CAP)


In this multicenter trial from The Netherlands, adults hospitalized with severe CAP were randomized to receive standard therapy with intravenously administered antibiotics for at least 7 days or to switch from the intravenous to the oral route of administration on day 3 of therapy if preset criteria for clinical stability were met. Most patients initially received monotherapy with either amoxicillin-clavulanate or a cephalosporin. More than 80% of patients had cases classified as pneumonia severity index class IV or V. Among the reasons for exclusion were cystic fibrosis and a need for mechanical ventilation. Pneumococcal infection was identified in one-fourth of patients; 11% were infected with an atypical pathogen. Eighty-one percent of patients assigned to switch treatment after 3 days did so; almost all switched to receive amoxicillin-clavulanate (500 mg/125 mg every 8 h).

In the intent-to-treat population of 265 patients, treatment failure occurred in 17% of patients in the intervention group and 15% of patients in the standard management group, a difference that was not statistically significant. There was also no significant difference between groups with regard to the number of patients who deteriorated or who died. The mean duration of intravenous antibiotic therapy was 3.6 days in the intervention group and 7.0 days in the standard group, and the total length of hospital stay was almost 2 days longer in the latter cohort.

It has become common practice at many US hospitals to “streamline” antibiotic therapy for patients hospitalized with CAP by switching early on from intravenous to oral administration. In fact, it is unclear to me why most patients need any intravenous therapy at all if, for example, a “respiratory” fluoroquinolone is chosen for treatment, because these each have bioavailability of >90% after oral administration. Nonetheless, it is generally standard that most patients receive at least their first dose of antibiotic intravenously—most while still in the emergency department and, with the new controversial pay-for-performance standard, within 4 h after arrival. Nonetheless, experience from nonrandomized studies has demonstrated the safety and efficacy of early switches, and the study by Oosterheert and colleagues has now demonstrated this in a randomized trial that included patients with high severity index scores. The overall mortality rate, however, was 5%—a lower figure than one would expect from the high severity scores at study entry, suggesting the possibility that the severity of illness may have been less than advertised.

The direct relevance of this study to clinical practice in the United States is uncertain, because that practice has, by and large, gone beyond the question addressed by these investigators. A recent, small, randomized study from The Netherlands found no difference in outcome among adults hospitalized with mild to moderately severe CAP who were treated with amoxicillin for a total of 3 days, compared with those who were treated for 8 days [1]. The current recommendation for the use of levofloxacin when given at a dosage of 750 mg daily is for a total of 5 days of therapy, regardless of the route of administration. Finally, the new micronized formulation of azithromycin has been approved in the United States for the treatment of mild-to-moderate CAP in a single oral dose.

There are at least 2 additional problems with regard to the applicability of these findings in the United States: very different practices, the longer duration of hospitalization in The Netherlands, and their standard use of antibiotic regimes without activity against atypical pathogens. This study, nonetheless, serves a purpose in that it may help to convince some individuals who may have been reluctant to switch to oral therapy relatively early in the course of treating moderately severe and severe CAP; however, clinical practice in many regions of the United States has moved beyond this point.

Reference


Immune Activation in Chronic HIV Infections: Is It the Gut?


Immune activation is a constant feature of untreated chronic HIV infection, and lymphocyte markers of activation correlate strongly with disease progression. In an unfortunate positive feedback system, such activation promotes productive infection of lymphocytes. During acute HIV infection, the virus itself undoubtedly plays the pivotal role in immune activation. This stage of infection is associated with rapid CD4 depletion that especially affects the lymphoid cells of the gastrointestinal tract, thus potentially compromising a mucosal barrier in direct contact with enormous quantities of bacteria. Brenchley and colleagues provide evidence consistent with their hypothesis that, during chronic HIV infection, translocation of microbial products from the gastrointestinal tract plays a pivotal role in producing systemic immune ac-
tivation and, thus, contributes to the progression of HIV infection.

Examination of plasma specimens obtained both from simian immunodeficiency virus (SIV)–infected macaques and from patients with chronic HIV infection identified increased concentrations of lipopolysaccharide (LPS), compared with controls, and the monocytes recovered from the patients were hyporesponsive to LPS, which is consistent with chronic exposure to this molecule. There was a significant positive correlation between plasma LPS concentration and the plasma concentration of IFN-γ, as well as between LPS levels and the frequency of circulating activated (CD38+ HLA–DR+) CD8 T cells. Administration of HAART was also associated with a reduction in the plasma LPS concentration. In addition, however, administration of antibiotics to SIV-infected macaques was associated with a reduction in the plasma LPS concentration. The authors, in consequence, conclude that “increased translocation of gastrointestinal microbial products directly contributes to systemic immune activation in the chronic phase of HIV infection and may ultimately determine the rate of progression to AIDS.” These extensive findings are provocative, and if the investigators’ interpretation is correct, they have important implications with regard to both therapeutic intervention and vaccine development.

**Bacteriophage on Your Food**

US Department of Health and Human Services, US Food and Drug Administra-

The US Food and Drug Administration has amended the food additive regulations “to provide for the safe use of a bacteriophage preparation on ready-to-eat meat and poultry products as an antimicrobial agent against *Listeria monocytogenes*” (p. 1). The product is a preparation of 6 *L. monocytogenes*–specific lytic phages meant to be sprayed on the surface of the food just before packaging.

**Recurrent Erythema Migrans (EM): Relapse or Reinfection?**


Some patients with classic Lyme disease may experience a subsequent recurrence of EM. Krause and colleagues aimed to prospectively determine whether such recurrences were due to relapse or to reinfection in Block Island, Rhode Island, where EM is highly endemic. They defined reinfection as having happened when EM occurred at a site remote from the previous EM lesion or if the episode occurred without detectable antibody to *Borrelia burgdorferi* between episodes. The occurrence of a new EM lesion at the same site as the previous one in a patient with persistence of antibody between episodes was considered to be a relapse.

Early Lyme disease was diagnosed 253 times among 213 subjects over a 14-year period, with 33 individuals experiencing 40 episodes of recurrent disease. Almost all patients with recurrent Lyme disease had received a standard course of antibiotic therapy for their prior episodes. The mean duration and symptom severity of recurrent episodes were similar to those of the initial episodes. None of the recurrences occurred in immunocompromised individuals. The mean interval between the first and second episodes was 43 months, and that between the second and third episodes was 38 months. There was no difference in seasonal distribution between initial and subsequent episodes; almost all episodes occurred during late spring and early summer, and individuals with recurrences reported more outdoor exposure and tick bites than did those without. On the basis of a priori criteria, all recurrences were judged to be the result of reinfection, rather than relapse.

This study is consistent with the observation that treatment of early Lyme disease with recommended standard antibiotic choices is highly effective with regard to pathogen eradication, but the initial infection does not provide immunity to prevent reinfection. Thus, in this prospective experience in an area of very high endemicity, recurrences of EM among patients who had received such therapy initially are the result of new exposures, not relapses of latent infection.

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