Fluoroquinolone Resistance in Salmonella: A Web Discussion

Rich Carnevale1, Kåre Mølbak2, Flemming Bager3, and Frank M. Aarestrup4

Web Discussion

Dr. Rich Carnevale of the Animal Health Institute (Washington, DC) was asked by Dr. Abigail Salyers, who runs the Reservoirs of Antibiotic Resistance (ROAR) web site, to comment on the article by Mølbak et al. [1] published in the New England Journal of Medicine in November 1999. Dr. Salyers requested that the article in the New England Journal of Medicine [1] be discussed, since it may have demonstrated a bridge between antibiotic use in animals and the selection effect of antibiotics. Therefore, the pigs might have acquired this strain from a multitude of sources, which might have rapidly become endemic in the herd with or without antibiotic use.

In one of the patients who died, Salmonella was not isolated from the patient at the time of laparotomy to repair a perforated intestine. She failed to respond to treatment with gentamicin and ceftriaxone; therefore, it is unclear whether antimicrobial therapy of any kind would have been effective. The ciprofloxacin MIC for this patient’s strain at the time of admission was not reported. In the other case, death occurred 2 months after the onset of the illness. This patient was obviously immunocompromised from diabetes, as well as from chemotherapy for cancer. It is impossible to determine from the report the true cause of death.

Furthermore, although the pathogens were quinolone-resistant, none showed clinical resistance to fluoroquinolones according to breakpoints for susceptibility tests of the National Committee for Clinical Laboratory Standards [1]. The authors speculated that the clinical impression suggested that ciprofloxacin did not appear to work as well as it should have, thus illustrating the complex nature of infectious disease. They even stated that “[i]t is important to emphasize that it would have been impossible to predict the clinical course of these patients even if they had been infected by a quinolone-sensitive strain.”

Response to Dr. Carnevale’s Comments by Dr. Mølbak, Dr. Bager, and Dr. Aarestrup

Some of the comments by Dr. Carnevale on the recent article in the New England Journal of Medicine [1] need correction.

Dr. Carnevale argues 4 points: (1) it is curious that the patients have consumed the pork “in a raw or near-raw state”; (2) there is no clear documentation that the use of antibiotics in these animals was responsible for the development of quinolone resistance; (3) the DT104 strain is spread clonally and may have been introduced in the herd with or without antibiotic use; and (4) there is no clear documentation of treatment failures. The following is our response.

Point 1. Over the years, several salmonella outbreaks have been associated with pork meat. Although some outbreaks have been related to specific products, such as sausages, ham, or smoked pork fillet, others have been associated with abattoirs that distribute various contaminated raw pork cuts, as was the case in the outbreak reported in the article in the New England Journal of Medicine [1]. In this type of outbreak, some patients may acquire infection by tasting or eating undercooked prod-
ucts (e.g., tasting a meatball before frying), whereas others may acquire infection by preparing a meal at home (or at storage in the refrigerator), which causes cross-contamination to raw products (e.g., salads or sauces).

Denmark is free of trichinosis, and domestic pigs in Denmark have been free of this disease since 1929. The prevalence of trichinosis among domestic pigs in the rest of Scandinavia is also very low. In Denmark, as in the rest of Europe, a number of pork products are eaten raw. One such famous example is the Italian parma ham, but there are many others (e.g., sausages that are not heat treated before consumption). Indeed, the reported DT104 strain outbreak is just one of several in Denmark in recent years that could be traced back to pork by using epidemiological methods and molecular typing of isolates for confirmation [2, 3]. The persons involved in the recent outbreak therefore should not be accused of atypical handling practices.

Points 2 and 3. These points boil down to arguing that the use of fluoroquinolones in animals has nothing to do with the emergence of resistant strains. Antibiotic drug resistance does not develop in a vacuum; it requires a selection effect of antibiotics at some point. There are several examples of the emergence of antibiotic-resistant bacteria transmitted from an animal reservoir to humans in relation to the use of antimicrobials in these food animals [4, 5]. Furthermore, there is recent evidence with regard to the use of fluoroquinolones that this process is ongoing for both Campylobacter and Salmonella [6–10]. With regard to S. typhimurium DT104, there is substantial evidence suggesting that once this phage type has become established it has the potential to spread clonally [11, 12]. We therefore agree with Dr. Carnevale that it may have become endemic in the swine herd without antibiotic use in that particular herd. For example, experience shows that trade in live animals is a major factor for spreading multidrug-resistant DT104 [12].

Point 4. The DT104 strain involved in the outbreak was resistant to nalidixic acid, and MIC of fluoroquinolones for the strain ranged from 0.06 to 0.12 mg/L, whereas fluoroquinolone MIC for nalidixic acid–susceptible strains are ≤0.03 mg/L. There are case reports and studies suggesting that fluoroquinolones may have an impaired effect for treating infections due to Salmonella strains that have been determined to be fluoroquinolone susceptible, by using break points, but that are nalidixic acid–resistant [13–16]. These strains often have only 1 mutation in the gyrA gene and will not be identified by susceptibility testing with use of fluoroquinolone disks or tablets. The strain involved in the outbreak reported in the article in the New England Journal of Medicine [1] is an example.

The reports suggesting a reduced effect of fluoroquinolones for treating infections due to these strains come not only from Denmark but also from Spain, the United Kingdom [14–16], and Vietnam (a study of invasive Salmonella typhi infections [13]). These reports all indicate that infections due to nalidixic acid–resistant Salmonella isolates may not be treated properly with fluoroquinolones at standard dosages. We therefore consider that clinical microbiologists should use nalidixic acid resistance as a marker for decreased fluoroquinolone susceptibility. Fluoroquinolones given orally may be bound in organic matter in the digestive tract. Therefore, MIC that are based on achievable concentrations in soft tissues are irrelevant to infections in the gastrointestinal tract.

It is, of course, impossible to predict the outcome of the infections in the 2 patients who died, assuming that they had been infected with a quinolone-susceptible strain. The ideal design for a study to determine the outcome of infections would be a double-blind trial in which patients were randomized into groups according to susceptible or resistant strains. Needless to say, this study would be impossible to conduct. Therefore, we are relying on observational data for quantifying the health impact of infections with resistant bacteria. The article in the New England Journal of Medicine [1] is an example of such a study, suggesting that fluoroquinolones may have an impaired effect in the treatment of infections due to nalidixic acid–resistant Salmonella. In 1 patient who died, for example, an intestinal perforation developed during treatment with ciprofloxacin. Later in the course, the patient received additional antimicrobial therapy. Therefore, it is not strange that Salmonella was not isolated from the samples obtained at that time. In many cases of severe salmonella infections, host factors may be of importance as co-determinants of clinical outcome, which is illustrated by the case of the other patient who died.

In summary, the Danish study published in the New England Journal of Medicine [1] suggests the following. First, antimicrobial-resistant bacteria are transmitted from a food animal reservoir (swine herd) to humans, in a situation with a modest selection effect of antibiotics. The documentation is unique because the authors were able to demonstrate the DT104 strain at several points along the food chain (in 2 pig herds, in meat samples from the abattoir killing pigs from these 2 herds, in retail outlets stocking meat from the abattoir, and in patients who purchased their meat supplies in the retail outlets).

Second, infections with the DT104 strain, which had a specific mutation in the gyrA gene, may have been associated with a poor response to fluoroquinolone treatment in some cases. Third, an effective salmonella surveillance and control program may identify and mitigate the spread of such bacteria. Because quinolone resistance will not develop without at least some selection effect of drugs and because outbreaks due to resistant bacteria may occur anywhere and thus pose a threat to public health, fluoroquinolones should not be used for treating animals used for human food unless other options have been ruled out. In these cases, they should be used only for treating a single animal.

Acknowledgments

We thank Dr. Abigail Salyers and ROAR (whose web site [www.roarantibiotic.org] and network are supported by the National Institute of Allergy and Infectious Diseases) for permission to publish the above comments.
References


