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Typhoid Fever in the United States and Antibiotic Choice

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In Reply: We agree with Dr Froehner that the potential relationship between age and prostate cancer survival may warrant further study. Although the randomized Scandinavian prostatectomy study by Bill-Axelson et al that Froehner cited may be interpreted as suggesting a potential relationship between age and cancer-specific mortality, the authors of that study noted that the effect was not statistically significant.[1] In addition, based on a previous study,[2] Bill-Axelson et al further noted that age was not an important prognostic factor in the population from which their study participants were recruited.[1]

These results are consistent with Froehner's conclusion that any relationship between age and cancer-specific mortality is controversial and unclear, and under these circumstances it should not be surprising that we did not observe an inverse relationship between age and cancer-specific mortality in our study. We agree that future studies could further explore any potential relationship between these factors but believe that, for now, the observation of improved outcomes following conservative management of clinically localized disease in more recent years, compared with earlier eras, may be the most important finding from our study for most physicians and their patients.

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Typhoid Fever in the United States and Antibiotic Choice

To the Editor: Based on the study of typhoid fever in the United States from 1996 to 2006 by Dr Lynch and colleagues,[1] it may not be appropriate to continue to recommend treatment with a fluoroquinolone (as the authors did) if nalidixic acid resistance and decreased susceptibility to ciprofloxacin is of concern, especially for persons who have visited South Asia. Almost 70% of the patient population in this study had visited India, Pakistan, or Bangladesh. Also, not all fluoroquinolones have the same effectiveness against enteric fever.[2,3] At Patan Hospital in Kathmandu, Nepal, where 5 to 10 patients with possible enteric fever may be seen each day during the summer months, ciprofloxacin is avoided for empirical treatment of enteric fever. Azithromycin is often used.[4]

Moreover, it is not known with what antibiotics these US patients were treated or what was their hospital course, in order to determine effectiveness. It seems likely that they received intravenous ceftriaxone and not a fluoroquinolone.

In addition, although this group of patients was limited to those with typhoid fever, for many clinicians typhoid and paratyphoid fever are confusingly interchangeable. Hence, a comment on the increasing incidence of paratyphoid fever (even in US travelers[5]) and the ineffectiveness of the present typhoid vaccine against paratyphoid organisms would have been useful.

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In Reply: Dr Basnyat's comments highlight many of the current challenges in antimicrobial therapy for patients with typhoid fever. Fluoroquinolones have been widely used; however, their effectiveness depends on the susceptibility of the patient's *Salmonella* ser Typhi isolate and the type of fluoroquinolone.[1] Gatifloxacin, a higher-generation fluoroquinolone, may be an alternative to older fluoroquinolones for *S* Typhi strains with decreased ciprofloxacin susceptibility.

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For patients with suspected typhoid fever in whom the probability of infection with a decreased ciprofloxacin susceptibility strain is low, fluoroquinolones may be started empirically and therapy continued if antimicrobial susceptibility testing confirms infection with a susceptible *S* Typhi strain. However, for typhoid fever patients in whom the probability of infection with a decreased ciprofloxacin susceptibility strain is high, such as those returning from South Asia or those in whom infection with a decreased ciprofloxacin susceptibility strain has been documented by susceptibility testing, an alternative therapy is warranted. Third-generation cephalosporins have been used in this situation, most commonly intravenous ceftriaxone. The oral third-generation cephalosporin cefixime has been associated with a high rate of clinical failures.[2] Recent studies have shown that azithromycin can also be used effectively for uncomplicated typhoid fever due to infection with decreased ciprofloxacin susceptibility *S* Typhi strains in endemic areas.[3]

Information on treatment is not collected as part of routine typhoid fever surveillance in the United States. However, Basnyat may be correct about the therapies of patients in our study. In a subset of typhoid fever patients at US sentinel sites for whom treatment information was collected through chart review, the proportion of patients who received a cephalosporin (86%) was higher than the proportion who received a fluoroquinolone (49%).[4]

Infections with *Salmonella* ser Paratyphi strains are indeed increasing in the United States and are the cause of a higher proportion of enteric fevers in Asia than previously thought.[5] Since 2008, surveillance for paratyphoid fever cases and antimicrobial susceptibility testing of *S* Paratyphi A and C isolates has been incorporated into national typhoid fever surveillance in the United States.

The similar clinical presentation of infection with *S* Paratyphi and *S* Typhi, as well as their similar antimicrobial resistance profiles, adds to the challenge of diagnosing and treating enteric fevers. It is also a reminder that among residents of endemic areas and travelers to those areas, prevention of infection with either agent is the best way to reduce disease burden. Typhoid vaccines are an increasingly important tool in typhoid fever control, especially in light of recent evidence demonstrating the indirect protective effects of Vi typhoid vaccine.[6] An effective vaccine for paratyphoid fever could play an equally important role. However, since available typhoid vaccines are not 100% effective and paratyphoid vaccines are still being developed, ensuring safe drinking water sources and improved sanitation in endemic areas remain cornerstones of worldwide prevention efforts for these diseases.

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Process Measures, Outcome Measures, and Heart Failure

To the Editor: The Commentary by Drs Fonarow and Peterson[1] presented a cogent picture of the current state of performance measurement. Performance measures are developed based on the best science available, but the science of measurement is evolving. Similarly, the underlying science delineating the critical steps in care is changing. The choice of measures must be derived from the underlying clinical evidence, and when steps are identified that ensure better patient outcomes, measures should be developed to augment or replace those in current use.

Neither outcome measures nor process measures by themselves are sufficient to achieve better care. Well-constructed evidence-based sets of process measures are proxies for good clinical outcomes. Risk-adjusted outcome measures are a rearview mirror for compliance with processes of care. Only by looking at the two together can conclusions be drawn about whether a particular outcome was the result of clinicians doing that which was important or whether assumptions about what would lead to better outcomes are incorrect.

Measures were never meant to be evergreen and should be changed as science changes, but before they are discarded, the effect on longitudinal trends and infrastructure should be considered. There is little formal agreement on which outcomes matter most, how to measure them in a reliable and valid manner, or over what time frame they should be measured. Mortality is important, but so are quality-adjusted life-years and health status. A variety of time frames—30 days, 60 days, 90 days, 1 year, 5 years—may be important. Studies have generally not correlated mortality with specific processes of care that might be improved in the same patient population.[2,3] The only study we are aware of that directly linked process measures with mortality in the same patient population (patients with heart failure)[4] came to a different conclusion than Fonarow and Peterson. That study found a direct positive relationship between these same 4 heart failure process measures and mortality.[4,5]

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