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Letter to the Editor

Drug resistance in typhoid in the new millennium

Dear Editor ,

A *25 year old lady was admitted with history of fever for 8 days. She has been having a few episodes of vomiting, and now a dry cough for 24 hours. She has been taking cefpodoxime with clavulanate twice daily for 4 days, with no benefit. Examination shows fever up to 105F, but no other findings. She is started on IV piperacillin-tazobactam and oral azithromycin. Blood cultures were sent.*

With the advent of antibiotics, many were quick to declare that the frontier of infectious diseases had been permanently won. The discoveries in this field were stellar- many new classes of antibiotics and a multitude of drugs in each class were identified in a very short period of time. Clinicians had a plethora of choice when it came to treating infections, that guidelines were required to help the clinicians choose the right drug- usually a problem of plenty. The good times, it seemed, would never end, as resistance was rare, and failure of therapy was usually attributed to a very sick patient, late presentation or poor immunity. The history of mankind, and science is particular is studded with poor judgement, non compliance with guidelines, and abuse of available resources. This has usually been rescued by ground breaking advancements, which are often serendipitous. Unfortunately, expecting a miracle to happen at every juncture of need may be overtly optimistic. This has also been the case with antimicrobial agents.

Both blood cultures grew Gram negative bacteria within 18 hours, later identified as Salmonella typhi. It was reported to be resistant to nalidixic acid, but susceptible to cephalosporins, quinolones, cotrimoxazole, azithromycin and chloramphenicol.

The treatment of typhoid provides an excellent case study to illustrate this point. In the 70s, the standard of care for treatment of typhoid was chloramphenicol or ampicillin. Both these agents were very effective, with resolution of fever noted in 48-72 hours in most patients. In the 1980s, reports of failure of therapy were being reported, and microbiologists noted resistance to chloramphenicol. At this point, quinoloes were being studied for this condition, and noted to be markedly effective.

Clinicians of the day hailed it as a break through in treatment, with response in as little as 24 hours. This lead to unbridled abuse of this class of antibiotics for all fevers, the majority of these being viral in nature, and not requiring any anti infective therapy. The vetenary industry were not to be denied as well, and they started use of this class of drugs for ensuring better health in the farm animals and to increase output. The drug was cheap, quite safe, with an oral and intravenous option- all the makings of a good drug, which was easy to abuse. The next decade and a half saw an exponential increase in use of this class, with the end result that there is widespread resistance to this class of antibiotics. Studies have shown that even if they appear to be susceptible in vitro, they fail when used in the patient, the phenomenon called NARST (nalidixic acid resistant *S.typhi*).

The situation was grim, as an important drug was lost in the war, but fortunately, clinicians understood the value of 3rd generation cephalosporins, chiefly ceftriaxone, in the struggle against typhoid. Widespread use of this class of antibiotics towards the end of the last millennium had disastrous consequences- the epidemic spread of extended spectrum beta lactamases (ESBLs) across the world, principally India, and, of course, progressive failure of that drug as well. Numerous centers now recognize that cephalosporin (and beta lactam) use has been associated with higher risk of clinical failure, and recommends it only as first line in pregnant women.

The patient continued on azithromycin and piperacillin-tazobactam for 5 days, but continued

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to have very high fever. She had severe nausea and vomiting, probably due to azithromycin and could not tolerate intravenous azithromycin either. She had a history of a drug rash with a sulfa drug, so cotrimoxazole could not be used. A repeat blood culture done on day 5 of treatment showed Gram negative bacteria, later identified as S.typhi.

Unfortunately, the current options for therapy in all infections, including typhoid are becoming more limited. The Infectious Diseases Society of America (IDSA) has declared this an emergent situation- bad bugs, no drugs. Others have gone so far as to predicting this to be the dawn of the next pre antibiotic era, somewhat similar to the situation nearly a hundred years ago. There is good reason for such pessimism. The pipeline of drugs is nearly dry. No new class of antibiotics against Gram negative pathogens is expected before 2020. At the current rate at which resistance develops, we will reach the point of infections due to bacteria with no known drugs long before that date.

The antibiotics were withdrawn, and she was started on chloramphenicol. She became afebrile in 36 hours, with cessation of vomiting and improvement in appetite. She was discharged home to complete the course of antibiotics, and to follow up for vaccination against typhoid.

We have now turned to older drugs discarded as "too toxic" to help rescue the situation. Colistin is a good example of an old drug which has made a resurgence thanks to the problem of severe drug resistance. Another example is the use of chloramphenicol in typhoid, as was seen in this patient, and the successful use of cotrimoxazole in patients with typhoid. Even these measures have limited benefit.

So, what is the road ahead? It does not appear very good. Those who do not learn from history are doomed to commit the same mistakes. It appears that unless we awake and act now, the situation is not salvageable.

1. Control of infections, and mortality to due infectious diseases was achieved a century ago in the United States, way before the introduction of antibiotics or vaccines. This was primarily due to public works like sanitation. Ensuring safe water supply and sewage disposal is the most important preventive step in control of infections.

2. Vector control for vector borne disease- most importantly mosquito control. The war against malaria was so nearly won in the mid 70s, but was soon out of control due to complacency. The most critical time in control of disease is at the fag end, when stamping out the last few cases can make the difference between success and failure.

3. Ensuring vaccination for vaccine preventable diseases like hepatitis B.

4. Control of drug use by antimicrobial stewardship and national antibiotic guidelines. The use of drugs in hospitals should be more tightly regulated, with higher antibiotics use only under expert supervision to ensure prevention of abuse. Microbiology labs should also be standardized to provide accurate information to clinicians to ensure that guidance is available.

5. Unfortunately, the bulk of antibiotic use happens outside the in patient. Out patient use of antibiotics should be discouraged when viral syndromes are suspected. The concept of over the counter purchase of antibiotics without prescription has to be abolished.

6. Regulation of the pharmaceutical industry and quality control of medications needs to be ensured, as quality of drugs is often considered suspect.

7. Antibiotic use in the animal husbandry industry has to be stopped immediately. This represents a huge volume of use, and contributes significantly to the problem of drug resistance in the community.

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