Research topics for undergraduates (2014-2015)

Modeling of antibiotic resistant bacteria.

Exposition

The problem of treating bacterial infections associated with surgical procedures and even common skin wounds has been getting considerable publicity as the number of cases and types of situations where resistance has been encountered increases. The *standard* stories, that bacterial infections were considered to not be a problem for a couple of decades and thus drug research and fundamental research ebbed, that there still is little incentive for the drug industry to develop new molecules because the financial payback is not nearly what can be obtained for drugs that treat chronic conditions, that existent is enhanced because antibiotics (ABs) are over-prescribed for illnesses for which they have no efficacy and that feeding ABs in large quantities to chickens, pigs and cows to increase weight gain and prevent at least some of the effects of overly-crowded conditions, are all probably true to some extent. However, evidence of resistance to penicillin was observed within a two years from its introduction (Appelbaum 2007, Clinical Infectious Diseases, 45:S165-70) which is perhaps due as much to the probability (Chen et al. 2013, Env. Sci. Tech. 47: 12753-12760) that at least some types of bacteria that were present in people who were treated even in these early years already had the genetic code for an enzyme to de-activate the β-lactam ring. In fact bacteria obtained from an isolated cave show considerable *multi-drug* resistance (Bhullar et al., PLOS One Vol. 7, April 2012, e34953) and even display a resistance mechanism that was not previously identified in "modern" bacteria.

Currently about 1 out 25 patients in US hospitals get nosocomial infections and the death rate is close to 10% of these patients. The types are split between pneumonia, surgical site, urinary tract, GI, central line and other infections. If the reason for hospitalization was nonelective, the threat of infection may be acceptable. However the problem of infection from resistant bacteria would seem to actually have a real "tipping point" if the surgery is not absolutely essential. For the past few decades significant advances in surgical techniques have made treatment of many conditions routine and outcomes (e.g., ACL reconstruction, "Tommy John", aortic valve replacement) very much better than the past and the associated hazard dropping continuously due to improved anesthesia drugs and techniques (among other reasons). While we have all probably known of someone, who has had the complication of a bacteria infection (e.g., Tom Brady, Rob Gronkowski,…) from routine surgery for a non life-threatening condition , in most cases, these people have fully recovered. However, if the infection rate for "elective" surgery reaches a critical value, perhaps 5% would be enough and if the death rate of these cases reaches a second critical value (again perhaps 5-10%), there would be a crisis in the surgical community. Of course physicians are smart and hospitals diligent so there has been considerable ramping up of procedures to prevent such infections. Still as the threat increases and the last line of defense weakens, the tipping point could be reached.

Possible topics to explore:

1. Mathematical modeling rate of resistance growth. While no doubt some work exists within biology that attempts to quantify the number and kinds of mutations that would be necessary to match a current animal (e.g., the development of modern dogs) from the ancestor species or explain how Japanese beetles have become almost completely resistant to *Sevin* (1-naphthyl methylcarbamate) in 40 years, has there really been useful research to explain the rate of MRSA development in the modern clinical environment? We know that some strains of bacteria likely to have been present in our guts had the genetic code for this, so was intra-species transmission of DNA the most important step or has it been evolution of *SA* strains? If different degrees of strain clearance occur, in various numbers of patients, is the number of predicted cases increased. How about assumptions about community and nosocomial origins of particular cases. There would seem to be almost unlimited numbers of problems that could be considered.
2. Analysis of multi, simultaneous treatments. Last fall a paper appeared in *Science Translational Medicine* (Imamovic and Sommer, 2013, Vol5 204ra132 1-10) that noted that two different drugs given simultaneously in certain circumstances worked better than either one individually. The study did not specifically identify mechanisms but it could be speculated that either that opening channels to pump one molecule out made it easier for another molecule to diffuse in, or that causing the bacterium to spend energy to defeat one mechanism left it with less energy to fight the other "battle". This work was not really all that new but apparently physicians don't know how to quantify this effect or what dose of pharmaceutical "A" that would be just enough to allow "B" to be increasingly effective. This effort would be data collection combined with mathematical modeling.
3. Most effective utilization of future drugs How should a new drug be used to (a) preserve its efficacy and (b) preserve the revenue stream that could lead to future drugs? (Actual research on monetization may not be out of bounds!) Should it be used only when a profile of the pathogens confirms that other treatments won't work, should it be treated as a "controlled-substance", should it only be given for an active infection or would it actually be more effective prophylactically?
4. Environmental incidence of antibiotics and transmission/ spread of resistant bacteria. This is an active research area elsewhere. To the extent that ABs are eluted through the kidneys of patients in a still active form and similarly through use in agricultural settings, what is the influence on environmental bacteria in terms of resistance? How do "they" get back into the human or animal infection cycle? Do they transmit genetic material that does come back? Or, for the bacteria within treated patients, are these really transmitted other than through acute symptoms (sneezing?) Many claims are made but which are the key steps?
5. Can we use thermodynamics in our favor to control virulent bacteria? It would be interesting to look at bacterial colonies and ultimately infected tissue in terms of the energy (i.e. nutrient and waste) fluxes to see if there is a way to put harmful bacteria at an *energetic* disadvantage — meaning that they are not as efficiently using available food sources as healthy tissue or non deleterious bacteria.? Will "turning off quorum sensing, if it can be done, contribute to this?