Impact of microbial resistance on clinical outcome and health expenses:

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Antimicrobial resistance is a prevalent and important problem worldwide. These infections are more difficult to treat than infections with similar organisms which are susceptible to commonly used agents, and effective therapy is often delayed. Infections with resistant organisms lead to adverse clinical outcomes, increased morbidity and mortality and are costly to the healthcare system. The magnitude of the adverse outcomes relate to the virulence of the organisms, the patient underlying condition, the syndrome, and the delay of appropriate therapy. Infections with resistant gram-positive, and gram-negative will be discussed along differences between various healthcare systems. Measuring and quantifying these effects is important both for resource allocation, and for designing strategies to combat resistance and improve patients' outcomes.

The importance of the comparison group in outcome studies:

The impact of microbial resistance on patients' outcomes may be compared to patients with infections with susceptible organisms or to patients who were at risk but have not developed infection. The comparison to infection with susceptible organisms assumes "replacement" i.e. what would be the impact of an infection if the causative organism is resistant rather than susceptible. The comparison to similar patient which did not develop an infection assumes "addition" or what would have happen to the patient if the patient did not develop an infection. The overall true world situation is a combination of both situation some infections with resistant strains are merely replacing susceptible strains in the event of inevitable infection (The doomed patient), while other infections would have not occurred if the organism were susceptible (e.g. surgical infections post surgical prophylaxis).

As a rule of thumb it has been suggested that replacement of an infection with susceptible organism with a resistant organism leads to 1.5-2 higher morbidity, mortality and cost.

This effect is of high magnitude when the infecting organisms is a virulent pathogen (e.g. S. aureus), when the affected patient is immune compromise, debilitated or severely ill, and when the infection is with high inoculum, hard to eradicate (abscess or foreign body) and at a high risk site (e.g. central nervous system or the blood).
The effect of Addition of infection (rather than replacement) is much greater, and vary dramatically depending on the type of infection.

Defining antibiotic resistance

Studies that have assessed the relationship between antimicrobial resistance and microbiologic fitness differ in their results. These differences are related to variability between the effects of various mechanisms of resistance on fitness, variability between strains of the same species, and methods of measuring fitness. In most cases when mutations leading to resistance are associated with reduced fitness, compensatory mutations that result in regained fitness arise. Resistant strains seen in the clinical setting are largely those able to both survive and effectively spread in high density antibiotic environment such as healthcare facilities and daycare centers; thus, they are well adapted organisms and are usually fitter than a random selection of strains belonging to the same species. Various mechanisms may lead to the same resistance phenotype, however their effect on the course of the infection may differ as some of the mechanisms may be more costly to the bacteria than others. Nevertheless, for epidemiological studies large number of cases have to be analyzed and differences in mechanisms of resistance are unlikely to be studied. Resistance may be coupled with virulence; transferable genetic determinants may co-transfer resistance and virulence, and the selection process within hospitals may co-select strains with both antibiotic resistance, epidemicity and virulence. Thus, it may be difficult to differentiate between the direct effect of resistance on patient outcome from the effects of the accompanied virulence factors.

Since antibiotic resistance is an ever changing target which varies in time and place, and since the type of anti-infectives used also vary, it is difficult to assess the outcomes associated with antimicrobial resistance and to generate data from which general

conclusions can be drawn. Alternatively, the outcomes of microbiologically inadequate treatment, defined as a mismatch between the spectrum of activity of the antibiotics used and the susceptibility of the organism cultured can be measured. This estimate provides a tool to calculate cost-effectiveness of various antimicrobial regimens among patients infected with variably antimicrobially resistant organisms.

Defining the outcome:

Mortality is often assessed however, it is the most extreme outcome, which may not be affected due to adequate response of the treating physician, but yet the patient may suffer severe adverse consequences related to resistance. For example, amputation of a limb may be performed to eradicate a severe infection which could not be cured by antibiotic treatment, indeed, this was found to be a life-saving procedure in patients with severe diabetic foot infection with pan-resistant bacteria. Thus, softer outcomes are required. Length of hospital stay, or intensive care unit stay are often used as a proxy to morbidity. Need for surgical procedures, and functional status at discharge are also an alternative. We suggested that cost of hospital stay is a very sensitive measure of morbidity, as it reflects the extra use of procedures, medications, imaging, and hospital facilities.

Economic impact of resistance:

The outcomes of antimicrobial resistance can be examined at various levels and from different perspectives for example the effect at the individual level vs. the public health level, from the perspective of the individual, the third party payer, or the society. Moreover, short-term outcomes can be examined versus long-term outcomes.

The economic outcomes are examined from the third party payer perspective. The societal, and individual perspectives are rarely, if ever examined since data on economic consequences to individuals, and to the society are very difficult to collect and to interpret. Moreover, decisions on antibiotic selection are not done by the patient, or society, but rather by third-party payers or care providers (i.e. hospitals).

Hospital costs are a useful outcome measure for an individual hospital as they best reflect the actual economic burden of the hospital; however, they can be difficult to

retrieve. In contrast, hospital charges are less reflective of actual cost, but are usually easy to retrieve from administrative databases and are consistent from patient to patient in most settings. They tend to be an overestimate of actual cost, although adjustment using cost-to-charge ratios can be performed. Resource utilization assesses more specifically what services or procedures are used by a patient. However, for comparative purposes, use of resources must be translated into monetary value. All of these economic measures of health care are not necessarily set by a market-based pricing system. The costs of care for a specific patient are artificial and arbitrary computations that may vary between sites and at different time periods.

Hospitals may use different ways to limit costs based on their method of reimbursement. For example, if reimbursement occurs *per diem*, the hospital will focus on reducing costly days of stay such as ICU or surgery days rather than the total length of stay, while if reimbursement occurs based on the diagnosis related group (DRG) or capitation, total expenses are the focus of cost reduction. The majority of studies that have evaluated the economic burden of resistance have been performed in the U.S. and, therefore, have measured total costs or charges. It is difficult to generalize on costs from one country to another. Even reporting lack common denominator. Thus, country specific, an even more importantly multinational studies are required to understand the economical impact of resistance.