The Ethics of Antimicrobial Use, AMS and Antibiotic Resistance

Charles Feldman
Deputy Chair
Human Research Ethics Committee
University of the Witwatersrand
The Pillars of Ethics

- Autonomy
- Non-maleficence
- Beneficence
- Justice

Garau J. Clin Microbiol Infect 2006; 12(suppl. 5): 16-24 (after Beauchamp and Childress)
Ethics and Infectious Diseases

- Infectious diseases have caused more morbidity and mortality than any other single cause, including war
  - Black death killed 1/3 of European population in 14\textsuperscript{th} century
  - TB has killed 1 billion people (1850 – 1950)
  - 1918 ‘flu killed between 20 – 100 million people
  - Smallpox killed 300 – 500 million people during the 20\textsuperscript{th} century alone
  - New infectious diseases are emerging in recent decades (HIV/AIDS, Ebola, SARS, Avian Influenza, H1N1, H7N9, MERS)
  - Antibiotics have saved ~80 million lives since 1940s

Selgelid MJ. Public Health 2009; 123: 255-259
Ethics and Infectious Diseases

• Infectious diseases raise difficult ethico-philosophical questions
  — surveillance, mandatory treatment, isolation/quarantine, vaccination

• The topic is closely connected to the topic of justice
  — malnutrition, sanitation, water, overcrowding, access to care, education (poverty)

• May promote fear, panic, stigmatization, discrimination, emotional and irrational decision making and policies

• Pose a threat to security of countries

Selgelid MJ. Public Health 2009; 123: 255-259
So are you Ready for A World Without Antibiotics?

• Antibiotics are the bedrock of modern medicine
• In the near future we are going to have to live without them once again
• And it’s going to be nasty
• 65 years ago David Livermore’s paternal grandmother died following an operation to remove her appendix – she succumbed to a series of infections that the pre-penicillin world had no drugs to treat

Sarah Boseley. The Guardian 12 August 2010
The Potential for a Tragedy - Antibiotics

• Appropriate antibiotic use presents a dilemma
• Can benefit individual patients but carry a cost to societal health by selecting resistant strains
• Mirrors what Hardin termed “the tragedy of the commons” – putting too many cows in a pasture will destroy it by overgrazing [overpopulation, shared fisheries] [driving a car – tax on carbon emissions]
• Protecting the antimicrobial commons, and hence the collective best interest, may require society sometimes to act against individual patient’s best interests – serious ethical concerns

Foster et al. Plos Medicine 2006; 3: 0177-0180
The Ethics of Prescribing Antibiotics

• Driving a car releases carbon dioxide which takes the world closer to global warming

• In such a situation there is often a call for taxes so that the person gaining the benefit pays costs equivalent to the damage they cause

• We are currently not paying the true costs of antibiotics and this encourages them to be used profligately
The Ethics of Prescribing Antibiotics

• If there was a world-wide tax ("sin tax") on antibiotics we may stop using them for viral infections and depending on the size of the tax may use them only for severe bacterial infections thus prolonging their length of activity

• The problems with "sin taxes" is that they may place the most unfair burden on the poorest

• They could be made "revenue neutral" or progressive so world’s poorest people are joint beneficiaries of the tax

http://blog.practicalethics.ox.ac.uk/2010
So, What is the Challenge?
Worldwide Impact of Resistance

- Worldwide burden of deaths from antimicrobial-resistant infections is estimated to be more than 700,000, mainly in low and middle income countries.
- In high income countries annual deaths from antibiotic-resistant pathogens are estimated at 23,000 in the USA and 25,000 in Europe.
- The excess costs of antibiotic-resistant infections is $20 billion/year.
- O’Neill report indicates that by 2050 there will be 10 million deaths per year and costs of $100 trillion.

Mechanisms of Antimicrobial Resistance

- **Efflux**
  - MexXY → aminoglycosides
  - MexAB → fluoroquinolones
  - AcrAB → biocides
  - RND → macrolides

- **PBPs alteration** → β-lactams

- **LPS modification** due to:
  - Peptide exposure or pH (PhoPQ and PmrAB)
  - Upregulation of LPS operon → polymyxin resistance

- **Outer membrane alteration** → biocides

- **Dysregulation of genes** after subinhibitory exposure → upregulation of resistance mechanisms → all antimicrobials

- **Point mutations** → mutator activity → Second step mutations for most antibiotics

- **Enzymes (β-lactamase)** → inducible by β-lactams → drug degradation

Fernandes L et al. Drug Resistance Updates 2011
Antibiotic introduced in clinical practice

- Aminoglycosides
- Quinolones
- Chloamphenicol
- Glycopeptides
- Tetracycline
- Penicillin
- Macrolides
- Trimethoprim
- Oxazolidinones
- Lipopeptides

Antibiotic resistance first described

1940s
1950s
1960s
1970s
1980s
1990s
2000s

TRENDS in Pharmacological Sciences
Stoking the Antibiotic Pipeline
Bad Bugs, No Drugs

As Antibiotic Discovery Stagnates ...
A Public Health Crisis Advances

And..........................No ESKAPE
And .................. No ESKAPE!

- **Enterococcus faecium**
- **Staphylococcus aureus**
- **Klebsiella pneumoniae**
- **Acinetobacter baumanii**
- **Pseudomonas aeruginosa**
- **Enterobacter spp.**
The More you use Them the More you Lose Them

• Unnecessary prescription hastens resistance
• Improper use hastens resistance
  – Antibiotic choice, timeliness, dose, routine, duration
• Agricultural use not harmless for humans
• Reducing use has a positive effect
• Political action may be needed!
The More you use Them the More you Lose Them

• Using the wrong drug for the wrong patient
• All antibiotic consumption (not just unnecessary use) helps select for antibiotic resistance
• Suboptimal dosing, even of the appropriate drug, can lead to resistance
• Non-compliance with the prescribed regimen

Niederman MS. Int J Antimicrob Agents 2005; 26: S170-S175
Why Antibiotic Resistance is an Ethical Dilemma

• There are ethical issues with accelerating antibiotic resistance

• Firstly, emergence of MDR and XDR infections accelerate the ethical challenges in treating infectious diseases – isolation against one’s will is a trade off between respect for individual autonomy and public good

• Secondly, fighting antibiotic resistance raises ethical questions about fair distribution of resources around the globe and while antibiotic use must be reduced in many countries around the globe, many people do not have ready access to effective antibiotics in the first place

http://www.reactgroup.org
Why Antibiotic Resistance is an Ethical Dilemma

- **Thirdly**, the extensive use of antibiotics in farming and need for AMS raises ethical concerns about wellbeing and appropriate treatment of farm animals and by the way we produce meat, but current farming practices are often only lucrative because the use of antibiotics keep infection rates low.

- This comes at cost of animal welfare and consumer safety when DR infections are transmitted in food.

- **Fourthly**, we have a moral obligation to future generations to protect the effectiveness of antibiotics and not leave a post-antibiotic world behind.

- Need to acknowledge these ethical issues and incorporate them into public discussion and policy.

http://www.reactgroup.org
What Are the Solutions to Antibiotic Resistance?

• Stimulate antibiotic development with incentives
  - Extent patent life
  - Better approval processes
  - Purchase commitments
  - Tax credits

• Use antibiotics more wisely
  - Impact on resistance development
  - Reduce pharmacy costs and toxicity
  - Reduce acquisition of potentially pathogenic bacteria
What about Antibiotic Stewardship?

• Whereas antibiotic resistance is inevitable, current rate and spread is not
• Challenge is to reduce total consumption of antibiotics as the only sure way to delay development of resistance
• Stewardship programs may be restrictive or educational
• Tend to encourage homogeneity in prescribing because of restricted formularies
The Ethical Dilemmas of Antibiotic Restriction

- Antibiotic restrictions present difficult choices and ethical considerations for physicians, patients and payers.
- **Physicians** must choose between welfare of the patient and directives of healthcare system to restrict antibiotic use [impact on their autonomy].
- These may be supported by incentives or penalties, causing a conflict of interest.
- **Patients** have an expectation of best care, but are often unaware of antibiotic restriction policies and therefore not fully informed about their treatment [lack of full informed consent].

Garau J. Clin Microbiol Infect 2006; 12(suppl. 5): 16-24
The Ethical Dilemmas of Antibiotic Restriction

• For **payers** the reduction of volume of antibiotics used or use of less expensive agents are attractive targets for cost saving

• [What about the **pharmaceutical industry**?]

• Only recently are we starting to understand the consequences of restricting antibiotics on costs and outcomes

• Balancing the risks of treatment with not treating with antibiotics is complex

• Suboptimal therapy that fails to eradicate the bacterial infections puts the patient at risk of poor outcome, adverse events and antibiotic resistance
The Ethical Dilemmas of Antibiotic Restriction

• Failure to treat where the risk of poor outcome exceeds the risk of an adverse event is not only unethical but also unacceptable.

• The key to rational antibiotic prescribing is to identify those patients who need antibiotic therapy and to optimise treatment to achieve the fastest bacterial and clinical cure.

Garau J. Clin Microbiol Infect 2006; 12(suppl. 5): 16-24
In clinical care it is important to distinguish between futile and marginal treatments.

Futile treatments are those that hold no prospect of achieving the intended outcome.

Bioethicists have largely abandoned the notion of futility after efforts to develop a clinically serviceable definition proved fruitless.

In reality, few treatments hold zero prospect of achieving the desired result.

Those that do rarely lead to clinical dilemmas.

Niederman MS et al. Crit Care Med 2010
Example is ventilated patient on 100% FiO2 and 15 cm PEEP who remains hypoxic

Because, in its most narrow sense, the goal of mechanical ventilation is to achieve satisfactory oxygenation, and it has not been able to do so in this example case, the ventilation may be considered “futile”

However, these situations of “physiological futility” are seldom troubling situations in ICU
Futility in Medical Care

- The challenges are where the effect of the intervention are uncontested but the benefit of the intervention are unclear.
- Example is a cardiologist not wishing to place a intra-aortic balloon pump in a patient with cardiogenic shock, not because it will fail to raise BP, at least for some time, but because no remedial benefit to the pump failure is possible or because the patient has poor clinical status – e.g. anoxic encephalopathy.
- Futility should be viewed in the overall context of the patient and not just from a physiological perspective.

Niederman MS et al. Crit Care Med 2010
Futile Care can Harm Others

• Conceivably at some stage antibiotic use could create completely resistant bacteria for which no other therapeutic resource exists

• Antibiotic allocation is not a zero-sum game as it occurs with typically limited resources

• This is potentially exponential and many studies indicate that mortality from ICU infection increases with inappropriate therapy and this is more likely to occur with MDR pathogens

• Antibiotics are among the least refused therapies

Niederman MS et al. Crit Care Med 2010
Futile Care can Harm Others

- Antibiotics are therefore atypical in this regard
- Their continued use in situations in which they no longer provide tangible medical benefit cannot be justified because of potential harm to others
- This type of futile care cannot be justified
- Physicians and patients have ethical obligations to desist from such marginal and symbolic use of futile interventions because of quantifiable collective harm

Niederman MS et al. Crit Care Med 2010
Antibiotic Misuse - Examples

• Using antibiotics for non-bacterial infection
• Administering an antibiotic “just in case”
• Wrong empiric antibiotic choice
• Underdosing antibiotics
• Using an antibiotic that does not penetrate to site of infection
• Using a second line antibiotic when a first line should be used
Reasons for Antibiotic Misuse

• Fear of Malpractice suits
• Lack of confidence in one's ability to diagnose infection
• Poor understanding of antibiotic PK/PD and spectrum of activity
• Lack of knowledge of sensitivity patterns (antibiogram) of the local community
• Erroneous concept that antibiotics are safe even if used when not needed
“[The physician] is under great pressure to prescribe the ‘newest’, ‘best’, ‘broadest’, antibiotic preparation, prescribe it for any complaint whatever, quickly, and preferably without worrying too much about specific etiologic diagnosis or proper identification of the drug”

Earnest Jawetz 1956
Conclusions of Talk

• Antibiotic misuse and overuse is driving antimicrobial resistance

• Antibiotic overuse and misuse is driven by clinician fear of litigation, patient pressure, clinical pathways and lack of confidence in ability to diagnose infection
  – Antibiotics are a clinicians security blanket

• It can be curbed by educating clinicians on making a proper diagnosis of infection, understanding appropriate empiric antibiotic choices
Most Overused Therapies

- Antibiotics
- Tranquilizers
- Sedatives
- NSAIDS
- Pacemakers
- Hysterectomy
- Upper GI scope
- Tympanostomy
The Drugs Don’t Work
The Drugs Don’t Work

I'm a level 65 Druid with Horticulture and Forest Feng Shui specialties.
Antibiotic resistance: a final warning

On Sept 16, the US Centers for Disease Control and Prevention (CDC) released its report *Antibiotic Resistance Threats in the United States, 2013*—their first ever report on this subject. From the outset the tone is clear: in his foreword, Tom Frieden, director of the CDC, states that “antimicrobial resistance is one of our most serious health threats. Infections from resistant bacteria are now too common”. The stated aim of this report is to increase awareness of the threat resistance poses and to encourage immediate action to address this threat.

To put the problem of resistance into perspective the report presents some sobering statistics. The CDC estimates that antibiotic-resistant organisms are the cause of infections in more than 2 million people each year in the USA. Of these people, more than 23,000 die as a consequence of their infections. The CDC stresses that these are conservative estimates and so the true numbers are probably much higher.

To further promote the risks posed by antimicrobial resistance the CDC will be holding its annual *Get Smart About Antibiotics Week* on Nov 18–24. This campaign will promote the appropriate use of antimicrobials across the USA and will coordinate with similar campaigns in Australia, Canada, and Europe. To coincide with these events, *The Lancet Infectious Diseases* will be publishing its commission on antimicrobial resistance.

Raising the profile of the problem of antimicrobial resistance is always welcome, but it begs the question of why we are still facing an issue identified decades ago? The report itself presents a timeline of emerging resistance, showing that reports date back to 1943. We are rapidly approaching the point when antimicrobial resistance will be nothing short of a catastrophe. And for the many thousands in the USA and elsewhere, the world’s response is already too late. However, momentum on this issue seems to be building. On Sept 19–20, there was a meeting of WHO’s Strategic Technical Advisory Group on antimicrobial resistance, with the purpose of identifying the key issues and options that will feed into a new global strategy. Hopefully, this will be more than the strong words we have become used to and will herald the beginning of robust action. ■ *The Lancet*