AVAILABILITY AND USE OF ANTIMICROBIALS FROM 1928 TO TODAY

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When did it all begin?

- Used by the ancients
  - Egypt: Garlic, willow, sycamore, acacia
  - India: Asafoetida (hing) which is sulpha-rich root
  - China

- 1600’s
  - Fungus used in topical wounds (Penicillim spp)
  - Herbal remedies (rich in flavenoids, condensed tannins)
Modern use

Thanks to PENICILLIN
...He Will Come Home!
Modern Antimicrobial Age

- 1928
  - Flemming describes inhibitory properties of penicillin.
  - Unable to isolate the compound
- 1940
  - Florey’s team mass produces penicillin
  - Effective in rodent model
- 1944
  - Pfizer manufactures penicillin in deep tanks
  - Streptomycin and terramycin follow
Human Infectious Diseases

1930
- Penicillin discovered

- First sulfonamide released

- Florey demonstrates penicillin's effectiveness

- Streptomycin, first aminoglycoside
- Chloramphenicol
- Chlortetracycline, first tetracycline

- Erythromycin, first macrolide

- Vancomycin

- Methicillin, penicillinase-resistant penicillin

- Gentamicin, antipseudomonal penicillin

- Ampicillin
- Cephalothin, first cephalosporin

- Penicillin-resistant infections become clinically significant

- Gentamicin-resistant Pseudomonas and methicillin-resistant staphylococcal infections become clinically significant
OVERLAPPING IN VITRO ACTION OF ANTIBIOTICS

Fig. 1. Diagram showing the types of infections in which the different antibiotics are most effective. (After Pulaski, Ann. N. Y. Acad. Sci. 53: 348. 1950.)
Antimicrobial Production

- Thousands of new antibiotics/antimicrobials
  - Difference in spectrum, safety and efficacy
- From millions of different soil samples
- Majority of fungal origin
- Has only left us with 20 major classes
  - Similar skeletons, similar mechanisms,
- All characterised by development of resistance
Modification around a skeleton
Veterinary Use: Food Animals

- Penicillin: reconstituted in water used for mastitis in latter part of war.
- Streptomycin was shown to be a growth promoter in chicks in 1946.
- 1949, chlortetracycline fermentation mash improved growth in poultry.
- Later as became cheaper, therapeutic use began
- 1950-1960: Food safety concerns were given consideration.
Veterinary Use: Small Animals

- Not surprisingly that use in small animal began soon after discovery
- Latter 1940’s: Dogs were being treated with streptomycin, sulphonamide, penicillins and/or aureomycin for pneumonias
- Also urolithiasis treated with surgical intervention and direct penicillin infusion
Food Safety concerns

- 1980’s and 1990’s
- Food safety based on MRL
  - Based on toxicity
  - Allergy potential?? (rare in food)
- More recently
  - Safety based on bacterial endpoints
Current Use of Antimicrobial

Companion Animals
- Therapeutic
- Prophylactic

Productions Animals
- Therapeutic
- Prophylactic
- Metaphylactic
- Growth Promotion (GP)

- Animal health uses 50% to 60% of all produced antimicrobials
- In the US, 33.33% used to enhance production (includes the ionophores)
Resistance

Emergence of drug-resistant bacteria

- Emergence of penicillinase-producing *Staphylococcus aureus*
- Emergence and spread of multidrug-resistant *S. aureus*
- Emergence of MRSA 1961
- Emergence of PISP 1967
- Emergence of penicillinase-producing *H. influenzae* 1974
- Emergence of PRSP 1977
- Emergence of BLNAR *H. influenzae* 1980
- Emergence of ESBL-producing Gram-negative bacilli 1983
- Emergence of VRE 1986
- Increased infections with MRSA, PRSP, BLNAR, 1990s etc.
- Increase of resistant gonococci
- Increase of MDRP 2000s
- Increase of quinolone-resistant *E. coli*

Development of antimicrobial agents

- 1928: Discovery of penicillin
- 1935: Discovery of a sulfonamide
- 1940s: Clinical application of penicillin
- 1950s: Discovery of aminoglycoside, chloramphenicol, tetracycline, and macrolide
- 1956: Discovery of vancomycin
- 1960: Synthesis of methicillin
- 1962: Synthesis of nalidixic acid

Development

- Development of first-generation cephems
  - Development of second-generation cephems
    - Development of third-generation cephems
      - Development of carbapenem and monobactam
      - Development of new quinolones

Increased use of third-generation cephem, carbapenem, oral cephem, and new quinolone antimicrobials

(Decrease in newly developed antimicrobial agents)
Development of resistance in food producing animals

Antibiotics for therapy, prophylaxis or growth promotion

Farm animals

- Feces
- Wildlife
- Soil
- Wastewater

Surface and Ground Water

- Grain, Fruits and Vegetables
- Household and Hospital Waste

Humans

Farm Workers

- Transport
- Slaughter
- Processing
- Handling
- Storing

Meat and Dairy Products

- Companion Animals

APAU, 2002
Consequences of in-food antibiotics

- Low chance of human toxicity – low absorption
- Possibility of transferable resistance
  - *Salmonella Typhimurium*
  - Vancomycin resistant enterococci
  - Erythromycin resistant staphylococci
  - *Campylobacter jejuni*
  - *Escherichia coli*
- Different regulatory approach: EU, FDA, etc
  - EU: prevent use
  - FDA: stringent control of use and availability (separate vet/medical therapeutic from AGP)
Growth Promoting Antibiotic: EU

- In the EU states
- 1971 – UK restricts use of compounds of human therapeutic value as growth promoter
- 1986 - Sweden prevents antimicrobial use for growth promotion
- 95 to 99 (EU states) Avoparcin, Spiramycin, virginiamycin, Zn bacitracin banned
- 2006 – EU stops all in-food growth promotors based on ‘precautionary principle’. Follows WHO recommendation
Life after the EU ban

- **Benefits**
  - Slight decrease in production in calves, pigs and fattening pigs
  - Increased investment in alternates (ZnO, enzymes)
  - Decrease in overall antibiotic utilisation
  - No increase in therapeutic use (except for Denmark).
  - Decrease in resistance in enterococci
  - Change in production practices of countries exporting to EU

- **Pitfalls**
  - Decrease in production in weaning pigs
  - Increased use in ionophors (necrotic enteritis in broilers)
  - Pastures contaminated with Zn
  - Increase in cost of production ($0.12/kg)
  - Costs of a trace-back system ($0.40/lb)
  - No decrease in human disease
Recent Trends

- Focus on good hygiene practices in production
- Antibiotics controlled by veterinarians
  - Focus on diagnosis
  - Therapeutic use promoted
- Follow prudent selection guidelines
  - Numerous guidelines available
  - Prophylactic/Metaphylactic should be avoided
Conclusion

- Antimicrobial been used since discovery
- Has been increased concerns in use
  - Divergence in veterinary and medical use
  - Increase precautions in food safety
  - Attenuated use in certain area
- Continues to be of clinical importance
  - Increasing need for quality protein production