The empiric antibiotic dilemma: Are we fueling antibiotic resistance?

KENYA PEDIATRIC ASSOCIATION, 2018
Antibiotic resistance fast facts...

- **$20/1.6€ billion** – Excess health care costs of resistant infections in the US/EU

- **8/2.5 million** – Excess hospital days caused by resistant infections in the US/EU

- **30%** - Antimicrobial component of pharmaceutical budget in the US

- **1.6%** - Antibiotic allotment of all drugs in development by major pharmaceutical companies

- **$1.1 billion** – Cost of unnecessarily prescribed antibiotics in the US

- **48%** - Proportion of US hospitals that have adopted stewardship policies
CAUSES OF ANTIBIOTIC RESISTANCE

Antibiotic resistance happens when bacteria change and become resistant to the antibiotics used to treat the infections they cause.

- Over-prescribing of antibiotics
- Patients not finishing their treatment
- Over-use of antibiotics in livestock and fish farming
- Poor infection control in hospitals and clinics
- Lack of hygiene and poor sanitation
- Lack of new antibiotics being developed

www.who.int/drugresistance

#AntibioticResistance

Emergence, Spread, and Environmental Effect of Antimicrobial Resistance: How Use of an Antimicrobial Anywhere Can Increase Resistance to Any Antimicrobial Anywhere Else

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Adequate empirical coverage

Induce antibiotic resistance
• Inadequate antibiotic therapy ➔ high mortality

• Broad spectrum antibiotics ➔ emergence/spread of antibiotic-resistant pathogens

*Clinical Infectious Diseases 2003; 36: 1006-12.*
Inadequate empirical treatment

The single most important independent determinant of mortality

Time of antibiotic initiation in septic shock

Hirani et al. University of Nairobi/Kenyatta National Hospital. 2017
Antibiotic use in septic shock - KNH

Hirani et al. University of Nairobi/Kenyatta National Hospital. 2017
Resistant pathogens: WHY??

- **Enterococcus faecium** – R to vancomycin (VRE)
- **Staphylococcus aureus** – R to methicillin (MRSA)
- **Enterobacter spp**. – R to carbapenem (CRE)
- **Acinetobacter baumanii** – R to carbapenems
- **Pseudomonas aeruginosa** – R to carbapenems
- **Enterobacter spp.** – R to 3rd gen cephalosporins
Non hospital compartment:
- community patients, food and wild animals and environment
- Antimicrobial resistance genes
- Resistant bacteria
- Antimicrobial use in the community patients and in food animals
- Antimicrobials in the environment

Hospital compartment:
- Antimicrobial resistance genes
- Resistant bacteria
- Antimicrobial use in the hospitals
How antibiotics act??

- Inhibition of cell wall synthesis
- Inhibition of protein synthesis
- Inhibition of nucleic acid replication and transcription
- Injury to plasma membrane
Resistance mechanisms...

• Destruction of antibiotics by β-lactamases

• Impermeability (closure of porin channels) ➔ resistance to carbapenems for Pseudomonas

• Extrusion by efflux ➔ resistance to multiple classes of antibiotics
<table>
<thead>
<tr>
<th>Type of β-lactamase</th>
<th>Classic microorganisms or types</th>
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<tbody>
<tr>
<td>Extended-spectrum β-lactamases</td>
<td><em>Escherichia coli</em></td>
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<tr>
<td></td>
<td><em>Klebsiella species</em></td>
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<td></td>
<td><em>Proteus species</em></td>
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<tr>
<td>AmpC</td>
<td><em>Serratia species</em></td>
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<td></td>
<td><em>Pseudomonas aeruginosa</em></td>
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<td><em>Indole + Proteus</em></td>
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<td></td>
<td><em>Citrobacter species</em></td>
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<td></td>
<td><em>Enterobacter species</em></td>
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<tr>
<td>Carbapenemases</td>
<td><em>KPC (Ambler Class A)</em></td>
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<td></td>
<td><em>NDM (Ambler Class B)</em></td>
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<tr>
<td></td>
<td><em>Oxa-type(^a)</em></td>
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<tr>
<td></td>
<td><em>(Class D)</em></td>
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ESBLs...

• Broad spectrum enzymes ➔ E.coli, Proteus, Klebsiella

• Change in only one amino acid in the β-lactamases

• Inactivate many broad spectrum β-lactam drugs

• Plasmid-mediated production

• Use of 3rd generation cephalosporin/fluoroquinolones ➔ risk factor for ESBL selection

In-vitro susceptibility NOT consistently predictive of clinical efficacy
Amp-C β-lactamases

- Chromosomally mediated production
- Occur in Pseudomonas aeruginosa and Enterobacter spp.
- Plasmid mediated in E.coli and Klebsiella spp
- One in $10^6$-$10^7$ organisms with a potential to produce this enzyme ➔ spontaneous mutation
- Mutant strains ➔ not competitive
- Injudicious antibiotic use ➔ clinical resistance during therapy

Crit Care 2016; 20:136
Ambler classification of $\beta$-lactamases

- Classes A, B, C, D

- Class B $\beta$-lactamases – initial carbapenemases
  Eg. New Delhi metallo - $\beta$-lactamase (Enterobacteriaceae)

- Class A – majority of ESBLs.
  Produced by Klebsiella pneumoniae

- Class D – produced by Acinetobacter spp

Carbapenemases not specific for carbapenems.
Ability to hydrolyze $\beta$-lactams of all classes

Defining features...

- Previous hospitalization within past 30 - 60 days ➔ resistant pathogens

- Invasive procedures ➔ colonization with MDR organisms

- Role of prior antibiotic usage ➔ risk of eliminating normal flora

- Severity of illness
What organisms need to be covered?

- Based on regularly updated data on trends/susceptibility
- Local microbiologic data
- Local data vary from unit to unit
- Unit-specific data is optimal
- Data as current as possible
Challenges??....Goal??

1. *Knowledge??

2. *Duration??

2. De-escalation after culture results

3. Culture results negative

4. Culture results indicating colonization?
Effective and timely treatment required

Empirical antibiotics are evidence based

Better diagnostics and education needed to target treatment
• ICU coverage of infections measured by ECI remains high (98%)

• 37-44% of treatment potential measured by EOI has been lost

• Without reserve drugs ECI will reduce.
Are we fuelling resistance??
Strategies to reduce resistance

• **Blast them!**
  Practice of using >1 antimicrobial agent to prevent emergence of resistance

• **Fool them!**
  Antimicrobial cycling or crop rotation

• **Stop irritating them!**
  Reduce antibiotics to bare minimum
Reducing antimicrobial selective pressure

• **Before therapy begins**
  Treat only those patients who are truly infected

• **During therapy**
  Avoid use of combination if single agent would suffice

• **At the tail end of therapy**
  Treat only for as long as is required
Antibiotics justified??

Yes....

1. Why?
2. What?
3. Where?
4. How?
1. When?
Thank you