Bridging Antibiotic Innovation and Access: Preserving the Power of Antibiotics

Open Session of the 24th WHO Expert Committee on Selection and Use of Essential Medicines
Monday April 24, 2023

Subasree Srinivasan, Medical Director, GARDP
All infections are treatable for everyone, everywhere

We work with partners to accelerate the development and access to treatments for drug-resistant infections
Accelerating late-stage development and access

**DEVELOPMENT**
Developing antibiotics through late-stage clinical trials to product launch

**ACCESS**
Improving access and appropriate use of antibiotics around the world
Building a portfolio
GARDP portfolio: aligned to the WHO Priority Pathogen List and covers 2 disease areas: Sepsis and STIs

Mix of NCEs and generic products

<table>
<thead>
<tr>
<th>Drug Product</th>
<th>Cefiderocol</th>
<th>Cefepime-taniboractam</th>
<th>Zoliflodacin</th>
<th>Flomoxef</th>
<th>Fosfomycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase</td>
<td>Approved</td>
<td>3</td>
<td>3</td>
<td>Approved</td>
<td>Approved</td>
</tr>
<tr>
<td><strong>Carbapenem-resistant Pathogens</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CRE, CRPA, CRAB</strong></td>
<td></td>
<td>POTENTIALLY ALL BL RESISTANT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>KPC, MBL, OXA RESISTANT</strong></td>
<td></td>
<td></td>
<td>NA</td>
<td>NA</td>
<td>WEAK CRE, CRPA, NOT FOR MONOTHERAPY</td>
</tr>
<tr>
<td><strong>3RD Gen Cephalosporin-resistant Pathogens</strong></td>
<td>ESBL-PE</td>
<td>ESBL-PE</td>
<td>Ceftriaxone-resistant *</td>
<td>ESBL-PE (EXCEPT AmpC)</td>
<td>ESBL-PE (EXCEPT AmpC)</td>
</tr>
</tbody>
</table>

* Neisseria gonorrhoeae ESBL (EXCEPT AmpC)
# Current Partnerships

**GARDP portfolio of NCEs and generic products**

<table>
<thead>
<tr>
<th>Drug Product</th>
<th>Cefiderocol</th>
<th>Cefepime-taniboractam</th>
<th>Zoliflodacin</th>
<th>Flomoxef (generic)</th>
<th>Fosfomycin (generic)</th>
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</thead>
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<tr>
<td><strong>Focus</strong></td>
<td>Sepsis</td>
<td>Sepsis</td>
<td>STI (gonorrhea)</td>
<td>Neonatal sepsis</td>
<td>Neonatal sepsis</td>
</tr>
<tr>
<td><strong>Originator (NCE)</strong></td>
<td><strong>Partner (generic)</strong></td>
<td><strong>Status</strong></td>
<td><strong>Class</strong></td>
<td><strong>Manufacturing right</strong></td>
<td><strong>Commercialization right, mainly LMICs</strong></td>
</tr>
<tr>
<td><strong>SHIONOGI</strong></td>
<td><strong>Venatorx</strong></td>
<td>Approved by FDA (2019) / EMA (2020)</td>
<td><strong>Siderphore</strong></td>
<td><strong>Yes</strong></td>
<td><strong>135 countries</strong></td>
</tr>
<tr>
<td><strong>Phase 3, ended March 2023</strong></td>
<td><strong>BL/BLI</strong></td>
<td><strong>Topoisomerase inhibitors</strong></td>
<td><strong>Yes</strong></td>
<td><strong>Generics</strong></td>
<td><strong>66 countries</strong></td>
</tr>
<tr>
<td><strong>Phase 3, ended March 2023</strong></td>
<td></td>
<td></td>
<td><strong>150+ countries</strong></td>
<td><strong>Generics</strong></td>
<td><strong>150+ countries</strong></td>
</tr>
<tr>
<td><strong>Approved in 4 Asian countries since 1988</strong></td>
<td></td>
<td></td>
<td></td>
<td><strong>Generics</strong></td>
<td><strong>135 countries</strong></td>
</tr>
<tr>
<td><strong>Approved in Europe and some LMICs</strong></td>
<td></td>
<td></td>
<td></td>
<td><strong>Generics</strong></td>
<td><strong>66 countries</strong></td>
</tr>
</tbody>
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**Class**
- Siderphore
- BL/BLI
- Topoisomerase inhibitors

**Manufacturing right**
- Yes
- (no right)
- Yes

**Commercialization right, mainly LMICs**
- 135 countries
- 66 countries
- 150+ countries
Addressing the most urgent threats to public health

**Children’s antibiotics and neonatal sepsis**
1 in 5 deaths due to antibiotic resistance concerns children.
200,000 newborns die each year from a resistant bacterial infection.

**Serious bacterial infections**
Patients undergoing common medical procedures, such as C-section, hip replacement, chemotherapy, or organ transplant, are at risk of acquiring bacterial infections that cannot be easily treated with commonly used antibiotics.

**Sexually transmitted infections**
Sexually transmitted infections caused by bacteria may become untreatable with the rise of superbugs, especially gonorrhea.
SEPSIS STRATEGY

Community Acquired infections

- Community acquired pneumonia
- Urinary tract infections
- Intra-abdominal infections
- Skin and soft tissue infections
- Sepsis of unknown origin
- Fever in neutropenic host

Hospital/healthcare associated infections

- Hospital and ventilator associated pneumonia
- Complicated intraabdominal infection
- Complicated UTI
- Catheter related BSI
- Post surgical wound infections

Neonatal sepsis

- Early onset
- Late onset (Hospital associated)

Includes adult and pediatric populations

Carbapenem sparing empiric regimens

Target 3rdG Ceph R Enterobacteria les

Target Carbapenem resistant Enterobacterial es and Acinetobacter and Pseudomonas

Improved benefit/risk (than polymyxins) empiric and targeted regimens
3rd Gen Cephalosporin resistant Enterobacterales infections
Current WHO recommendation for mild-moderate intra abdominal infections

**APPENDICITIS**

All dosages are for normal renal function. Antibiotics are listed in alphabetical order and should be considered equal treatment options unless otherwise indicated.

**First Choice**
- Amoxicillin + clavulanic acid 1 g + 200 mg q8h IV OR 875 mg + 125 mg q8h ORAL
- Cefotaxime 2 g q8h IV OR
- Ceftriaxone 2 g q24h IV OR

**Second Choice**
- Ciprofloxacin 500 mg q12h ORAL
- Metronidazole 500 mg q12h ORAL

Ciprofloxacin and metronidazole have excellent oral bioavailability and the IV route should be reserved for patients with impaired gastrointestinal function.

**COMBINED WITH**
- Metronidazole 500 mg q12h IV/ORAL
  - Oral weight bands: 20-40 kg = 500 mg, 40-80 kg = 1 g
- Ceftriaxone 1 g q12h IV

**Second Choice**
- Amoxicillin IV
  - 1st week of life: 50 mg/kg/dose q12h
  - > 1st week of life: 30 mg/kg/dose q12h

**COMBINED WITH**
- Ciprofloxacin 150 mg/kg/dose q12h
  - Oral weight bands: 20-40 kg = 100 mg, 40-80 kg = 200 mg

**Contraindicated in**
- Ciprofloxacin and metronidazole have excellent oral bioavailability and the IV route should be reserved for patients with impaired gastrointestinal function.

**CHOLECYSTITIS**

Consider meropenem only in complicated cases if there is a high risk of infection with ESBL-producing Enterobacterales.

**DIVERTICULITS**

Severity | Adults | Total treatment duration
---|---|---
Mild cases | First choice Amoxicillin + clavulanic acid IV: 1 g + 200 mg given every 8 hours OR Cefotaxime 1 g given every 8 hours OR Ceftriaxone (IV): 2 g given once a day AND Metronidazole (IV): 500 mg given every 8 hours | Continue for 4 days after control of the source of infection is achieved provided that there is good clinical recovery.

Oral 825 + 125 mg given every 8 hours OR Ceftriaxone (IV): 2 g given once a day AND Metronidazole (IV): 500 mg given every 8 hours OR Ceftriaxone (IV): 2 g given once a day AND Metronidazole (IV): 500 mg given every 8 hours

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Oral 825 + 125 mg given every 8 hours OR Ceftriaxone (IV): 2 g given once a day AND Metronidazole (IV): 500 mg given every 8 hours
Current WHO recommendations for mild upper urinary tract infections

<table>
<thead>
<tr>
<th>Severity</th>
<th>Adults</th>
<th>Children</th>
<th>Total treatment duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild to moderate</td>
<td><strong>Ciprofloxacin</strong>&lt;sup&gt;ab&lt;/sup&gt; (oral): 500 mg given every 12 hours</td>
<td><strong>Ciprofloxacin</strong>&lt;sup&gt;1&lt;/sup&gt; (IV/oral): 15 mg/kg/dose given every 12 hours</td>
<td>7 days&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>cases</td>
<td>(Ciprofloxacin has excellent oral bioavailability and the IV route should be reserved for patients with impaired gastrointestinal function.)</td>
<td>Oral weight bands: 3–&lt; 6 kg: 50 mg given every 12 hours 6–&lt; 10 kg: 100 mg given every 12 hours 10–&lt; 15 kg: 150 mg given every 12 hours 15–&lt; 20 kg: 200 mg given every 12 hours 20–&lt; 30 kg: 300 mg given every 12 hours ≥ 30 kg: use adult dose (Ciprofloxacin has excellent oral bioavailability and the IV route should be reserved for patients with impaired gastrointestinal function.)</td>
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Consider gentamicin or amikacin where ESBL producing isolates are highly prevalent.
Pathogen-attributable fraction of deaths attributable to bacterial AMR for the six leading pathogens by GBD super-region, 2019: Mortality attributable to AMR in E.coli is considerable across all regions.
High attributable mortality due to fluoroquinolone or 3G cephalosporin resistance in *E. coli*

Sequencing of Antibiotics with Escalating AMR

Effective carbapenem-sparing ‘WATCH’ options (such as forgotten antibiotics) could

• Influence downstream development of carbapenem resistance
• Reserve RESERVE agents for infections with the highest levels of resistance

ACCESS
CEFTRIAXONE

WATCH
MEROPENEM

RESERVE
CEFTAZ-AVIBACTAM
Re-development of existing generic antibiotics

Optimising antimicrobial use in humans – review of current evidence and an interdisciplinary consensus on key priorities for research

Esmita Charani, PhD1.5,*, Martin McKee, DSc2,*, Raheelah Ahmad, PhD3, Manica Balasegaram, MD4, Candice Bonacousa, MSc5, Gemma Buckland Merrett, PhD6, Reinhard Busse, MD7, Vanessa Carter8, Enrique Castro-Sanchez, PhD1, Bryony D Franklin, PhD9,10, Pantelis Georgiou, PhD11, Kerri Hill-Cawthorne, MSc1, William Hope, PhD12, Yuichi Imanaka, MD13, Andrew Kambugu, MMED14, Andrew JM Leather, FRCS15, Oluchi Mbamalu, PhD5, M McLeod, PhD1,10, Marc Mendelson, PhD5, Mirfin Mpundu, DrPH16, Timothy M Rawson, PhD1,17, Walter Ricciardi, MD18, Jesus Rodriguez-Manzano, PhD11,19, Sanjeev Singh, PhD20, Constantinos Tsioutis, PhD21, Chibuzor Uchea, PhD6, Nina Zhu, PhD1, Alison H Holmes, MD1,***

“A major driver of AMR and poor clinical outcomes is suboptimal antimicrobial use. Current research in AMR is inequitably focused on new drug development. To achieve antimicrobial security we need to balance AMR research efforts between development of new agents and strategies to preserve the efficacy and maximise effectiveness of existing agents.”

E. Charani et al. / The Lancet Regional Health - Europe 00 (2021) 100161
Re-development of existing generic antibiotics

Forgotten Antibiotics: An Inventory in Europe, the United States, Canada, and Australia
Céline Pulcini, Karen Bush, William A. Craig, Niels Frimodt-Møller, M. Lindsay Grayson, Johan W. Mouton, John Turnidge, Stephan Harbarth, Inge C. Gyssens, the ESCMID Study Group for Antibiotic Policies

Essential and forgotten antibiotics: An inventory in low- and middle-income countries
Gianpiero Tebano, Grace Li, Bojana Beovic, Julia Bielicki, Adrian Brink, Mushira A Enani, Brian Godman, Sylvia Lemos Hinrichsen, Dan Kibuule, Levy-Hara Gabriel, Oyinlola Oduyebo, Mike Sharland, Sanjeev Singh, Heiman F L Wertheim, Dilip Nathwani, Céline Pulcini; European Society of Clinical Microbiology and Infectious Diseases Study Group for Antimicrobial Stewardship
Forgotten generic antibiotics: key features

Forgotten generic antibiotics can:

• Have a role in daily practice in different clinical situations:
  • Enabling reduction in the use of other broader spectrum antibiotics
  • Offering additional treatment options to treat MDR pathogens
  • Acting as niche agent for specific pathogens, when applicable

• Be of added value particularly in LMICs, where prevalence of MDR bacteria is often very high, calling for effective treatments that are cost friendly.

Key characteristics that leads to a vicious cycle promoting limited use:

Mainly out-of-patent products → Low level of scientific evidence (particularly on PK/PD and clinical efficacy) → Low availability (often registered in just a few countries, limited market size) → Low use by physicians and absence of inclusion in guidelines → Mainly out-of-patent products

In conclusion,

• Inclusion of these forgotten antibiotics with specific utility in today’s context of increasing AMR on the WHO-EML/EMLc could in fact break this vicious cycle and improve the availability of these agents resulting from increased interest by generic manufacturers.

• Sustaining supply chains for forgotten antibiotics will require indications that can meet requirements for optimal volumes of production.
GARDP proposal for consideration of inclusion of forgotten generic antibiotics on the EML/EMLc

• Forgotten generic antibiotics:
  • Fill an unmet need
  • Can potentially have an impact on overall AMR patterns in a region
  • A cost effective solution

• Provided they:
  • Meet current PK-PD dosing standards
  • Demonstrate relevant *in vitro* activity against the target pathogen/s in the regions of interest
  • Have a favorable benefit-risk assessment for the indications under consideration as evidenced by safety data and inclusion in local treatment guidelines
  • Meet current standards for quality assessment

Inclusion in the EML is the “first step in the policy process towards assuring access to these medicines”

Current application A.17 to EML/EMLc for flomoxef sodium

- Is a cephemycin active against ESBL-producing Enterobacterales approved in 1988 for adults and children for a large range of bacterial infections in Japan
- Could be a good option for empiric treatment of mild to moderate intra abdominal and upper urinary tract infections, particularly given the unmet need due to increasing levels of resistance to first line antibiotics in E. coli globally
- Is an older and forgotten antibiotic, which retains some unique properties
  - Make it a worthwhile consideration despite clinical evidence of efficacy being generated against a different standard of rigor compared to current drug development methods
  - Limited availability: registered in Japan, S Korea, Taiwan and PRC.
- Recent data:
  - Updated PK-PD modeling and associated dosing recommendations allow for a high probability of target attainment and is an important piece of drug development that should be considered when evaluating the evidence
  - Continued activity of flomoxef against contemporary clinical strains of Enterobacterales provides further support for its adoption.
Thank you