Egyptian Drug Authority
Pharmaceutical Care Central Administration
General Administration for Drug Utilization & Pharmacy

هيئة الدواء المصرية
الإدارة المركزية للرعاية الصيدلية
الإدارة العامة للممارسات الدوائية والصيدلية

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PHARMACY PRACTICE & DRUG UTILIZATION

ANTIMICROBIAL NEWSLETTER

Treatment approaches for MDROs series

As the world struggles to take a breath amid the current COVID-19 pandemic, the antimicrobial resistance amongst previously treatable pathogens continues to grow in an alarming rate. Unfortunately, the rate of new antimicrobial discoveries falls far behind, leaving us with limited treatment options for extensively resistant pathogens.

In order to promote the research and development of new antibiotics, the WHO has published a list of antibiotic-resistant "priority pathogens" – a catalogue of 12 families of bacteria that pose the greatest threat to human health.

⇒ In this series, we shed the light on the treatment approaches of the Multi-Drug Resistant Organisms (MDROs) in WHO Critical-priority list.

WHO Critical-priority list

- **Acinetobacter baumannii, carbapenem-resistant.**
- **Pseudomonas aeruginosa, carbapenem-resistant.**
- **Enterobacteriaceae, carbapenem-resistant, ESBL-producing.**

Series 1:- Carbapenem-resistant Acinetobacter baumanii (CRAB)

CRAB is a healthcare-associated pathogen that commonly cause Ventilator-associated-pneumonia (VAP) and Blood-stream Infections (BSI). It is well-known for its ability to acquire resistant genes and can rapidly develop into Multi-drug-resistant (MDR), Extensively-drug-resistant (XDR) or even Pan-drug-resistant (PDR).

Resistance Mechanism

1) Production of Extended Spectrum Beta-Lactamases (ESBLs)
2) Production of AmpC cephalosporinases
3) Production of serine-based metallo-requiring and OXA-48 carbapenemases
4) Production of aminoglycoside-modifying enzymes
5) Change in drug-target binding sites
6) Presence of efflux pumps
7) Mutant porins proteins with subsequent decrease in outer membrane permeability.

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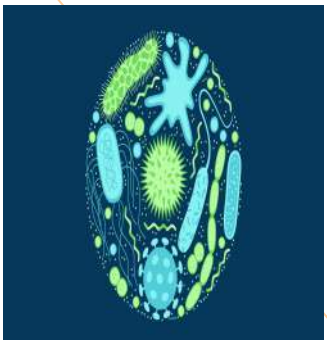
Inside this issue:



CRAB treatment

Currently, a consensus recommendation regarding the optimal treatment for XDR A. baumanii has not been established.
So far, Colistin is considered the backbone of treatment, yet the debate whether to use it alone or in combination with other agents is still ongoing.
According to the International Consensus Guidelines on the Optimal Use of the Polymyxins:
1) For Invasive infections, Colistin should be used with one or more additional agents to which the pathogen displays susceptible MIC.
2) If second agent with susceptible MIC is not available, Colistin should be used as monotherapy.
However, the consensus ranked their monotherapy recommendation weak, due to opinions division between the panel members. Many members were concerned that monotherapy confer the risk for resistance development.

Current randomized clinical trials (RCTs) for Colistin combination therapy with either Meropenem, Rifampicin, Fosfomycin, or Tigecycline have failed to demonstrate improved outcomes (i.e. 30-day mortality) compared to monotherapy, despite showing higher microbiological response.

Further in-vitro data suggests high-dose Sulbactam (e.g. 3 g IV over 4 hours repeated every 8 hours) as a possible candidate for combination, given its intrinsic activity against A. baumanii and possible synergistic effect with Colistin.

Nevertheless, clinical trials evaluating different antibiotic combinations for XDR and PDR A.baumanii are scarce, and most of them are based on observational studies and in-vitro data.

CRAB quick facts

1) Do not substitute a Carbapenem for another without testing.
2) Acinetobacter is intrinsically resistant to Ertapenem.
3) Avoid Piperacillin-tazobactam. May be active in vitro but fail clinically.
4) Tigecycline is not recommended due to sub-therapeutic serum conc. In bacteremia plus increased risk of all-cause mortality compared with other agents.

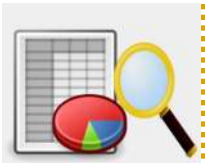
In conclusion, double-blinded RCTs are still needed to evaluate the impact of combination therapy on CRAB treatment, until then, monotherapy VS combination therapy remains an unanswered question.

Measurement of antibiotic use

- Antimicrobial resistance (AMR) is a global crisis that affects our ability to treat common infections and threatens our existence.
- Although the emergence of AMR is a complex multifactorial process, misuse and overuse of antimicrobials remains one of the most important factors that we can control to tackle resistance.
- In order to improve the quality of prescribing and develop effective policies and interventions that optimize the antimicrobial use, we must collect data about the actual situation.
- There are two main types of measurements of antibiotics: Quantitative and Qualitative approaches.

Quantitative approach

- It shows how many antibiotics are being used, using a standard international surveillance measure: e.g. Defined Daily Dose (DDD) and Days Of Therapy (DOT) .
- DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults.
- DOT is Aggregate sum of days for which any amount of specific antimicrobial was administered to individual patients.



Qualitative approach

- It provides information on types of antibiotics that are being given to patients, their indication, their use for treatment of particular infections and shows whether these antibiotics are being prescribed in accordance with local prescribing guidelines.
- This type of qualitative information can be collected in a structured way using Point Prevalence Surveys (PPS), which can then be fed back to prescribers to define areas for improvement.

Point Prevalence Survey (PPS)

A data collection tool used to identify the number of people with a particular disease or condition at a specific point in time.

It could provide a snapshot, of the proportion of the population with a healthcare-associated infection or receiving antimicrobial agent at the time of the survey.

Point prevalence studies (PPS) have a well-established methodology to measure the prevalence of antimicrobial use and HAIs in hospitals. Results of PPS can be used to evaluate quality indicators, to follow-up antimicrobial stewardship and infection control programs, and to support decision-making.

<u>Different protocols/methodologies of PPS:-</u>

- Global PPS project from University of Antwerp: Used in over 80 countries worldwide.
- WHO PPS Methodology: Implemented in 34 countries in 3 WHO regions as of April 2021.
- ECDC protocol for Point Prevalence Survey of healthcare associated infections and antimicrobial use
- US Centers for Disease Control and Prevention protocol
- Medicines Utilization Research in Africa (MURIA) protocol
- Antibiotic Resistance and Prescribing in European Children (ARPEC).

PPS History

Global PPS

* ESAC-PPS: European Surveillance of Antimicrobial Consumption

** ARPEC-PPS: Antimicrobial resistance and prescribing in European Children

EU point prevalence survey

WHO PPS

Objectives of different PPS

ECDC

1. Estimate the total burden of HAIs and antimicrobial use.
2. Describe patients, invasive procedures, infections and prescribed antimicrobials.
3. Disseminate results to those who need to know at local, regional, national level.
4. Identify targets for quality improvement.

G-PPS

1. Identify burden.
2. Change practice.
3. Measure impact.

WHO

1. Provide a standardized methodology for use in low-, middle- and high-income countries.
2. Collect information on the prescribing of antibiotics.
3. Support policy-makers and practitioners for improving antibiotic use.
4. Provide a standardized tool for hospitals.

Advantage of WHO methodology

WHO methodology provides a more suitable option for Low-Middle income countries (LMIC). The reason behind this is that it divides variables into core variables (E.g., measuring antibiotics) and optional variables (e.g., measuring antifungals), depending on the available resources and information in LMIC.
Thus, it reflects the need of the LMIC while maintaining the comparability of their data with those of High-income countries.

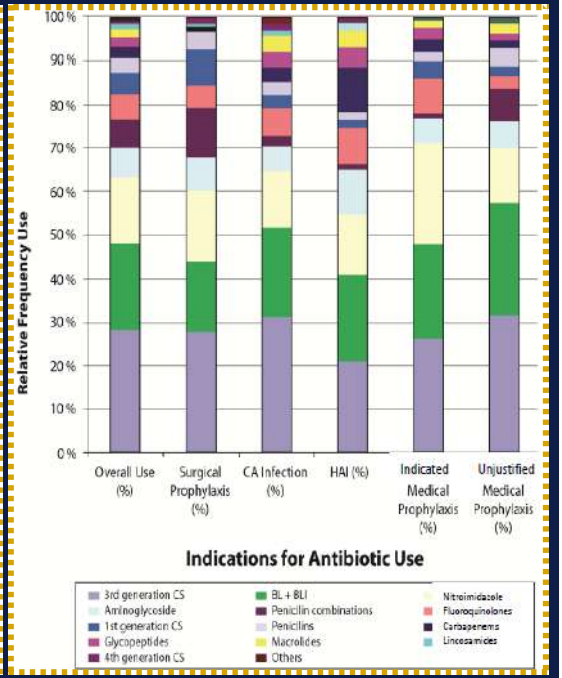
Egypt and PPS

A Point Prevalence Survey of Antibiotic Use in 18 Hospitals in Egypt

A point prevalence survey was conducted in 18 hospitals in March 2011. The 18 participating hospitals included five Ministry of Health and 13 university hospitals.

The methodology and definitions used for the prevalence survey were adopted from those used by the European Surveillance of Antimicrobial Consumption (ESAC) Project. Data were collected using two standardized forms.

Results indicate that third generation cephalosporin were the most commonly prescribed antibiotics (28.7% of prescriptions). Penicillins with beta-lactamase inhibitors and mitronidazole derivatives accounted for 19.7% and 15.2%; respectively,

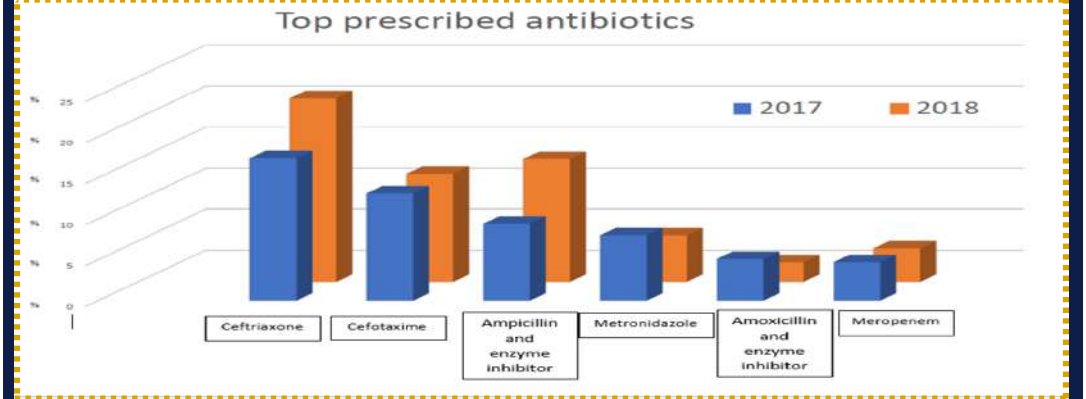


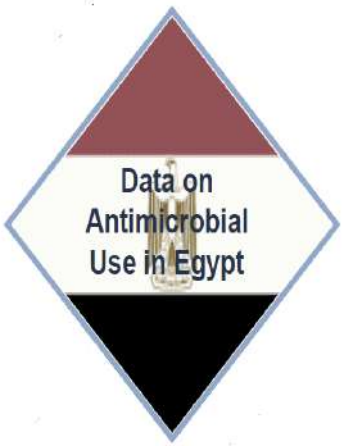
Egyptian Experience using G-PPS tools

First Wave (2017) conducted in 17 hospitals from different directorates, sectors, and institutions.

Second Wave (2018) Conducted at 41 hospitals from different sectors, directorates, and institutions.

Results indicate that Beta-lactams anti-bacterial were the most prevalent antibiotics used . The most commonly used beta-lactams classes were combinations of penicillins+ beta lactamase inhibitors and third generation cephalosporins.





Third Wave (2019) conducted in 5 pilot hospitals plus 4 additional enthusiastic hospitals in 4 different directorates.

Fourth Wave:- Evaluation of 5 pilot hospitals to assess weakness points, then a training is provided in July 2021.

EDA Initiative

- EDA initiative is a mega project conducted in 2021 that aims to provide pharmacists, either as individuals or in hospitals, with updated information in different aspects (e.g. Antimicrobial Stewardship). It also aims to standardize pharmacy practice between Egyptian pharmacists. Participating hospitals were also provided with additional quality sessions and are required to conduct improvement projects. These projects will be evaluated, and a winner will be chosen.
- The initiative consisted of five programs:-

1. Antimicrobial program (Individual/Hospital)
2. ICU Program (Individual/hospital)
3. Oncology Program (Individual/Hospital)
4. Pharmacy practice program (Individual)
5. Patient Counseling Program (Individual)

- In order to provide an interactive learning experience, virtual zoom lectures were provided, recorded and uploaded to an online platform (Link Zone). Pre-tests and Post-tests were held to evaluate the learning outcomes.
- A total of 6698 pharmacists have participated in this Initiative.

Antimicrobial Program

- EDA Antimicrobial rational drug use aims to raise awareness of antimicrobial resistance and to implement antimicrobial stewardship programs in all participating hospitals.
- Online zoom sessions were provided over 3 weeks (individual program) and 5 weeks (Hospital program).
- Currently a total number of 55 are carrying out their improvement projects.

Program ILOs

1. Understand antimicrobial stewardship, purpose, main goals, barriers to ASP implementation, and different types of measures in ASP programs.
2. Understand the ATC system .
3. Identify and compare different measures of quantitative antimicrobial use as DDD system.
4. Recognize MDROs and Antimicrobial resistance types.
5. Recognize the importance of antimicrobial use surveillance, and identify the steps to plan and carry out PPS.
6. Identify antimicrobial spectrum, and recognize most common infectious diseases and their management, also define therapeutic effects, side effects, and administration routes of major antibiotics
7. Define the antibiogram, its importance, its uses, and how to overcome challenges in the preparation of a cumulative antibiogram
8. Know the purpose and goals of WHO AWaRe categorization.

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