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MULTIDRUG-RESISTANT ORGANISMS IN URINARY TRACT INFECTIONS IN CHILDREN

DR.REZA DALIRANI

PEDIATRIC NEPHROLOGIST

MOFID CHILDREN HOSPITAL

INTRODUCTION

- ANTIMICROBIAL RESISTANCE REPRESENTS A GLOBAL HEALTH CRISIS AND ONE OF THE MOST SERIOUS THREATS HUMANS FACE TODAY.
- SOME BACTERIAL STRAINS HAVE ACQUIRED RESISTANCE TO NEARLY ALL ANTIBIOTICS.
- IN 2017, THE WORLD HEALTH ORGANIZATION (WHO) HAS PUBLISHED A LIST OF ANTIBIOTIC-RESISTANT PRIORITY PATHOGENS, THE LIST IS CATEGORIZED AS CRITICAL, HIGH, AND MEDIUM PRIORITY, IN ORDER TO GUIDE AND PROMOTE RESEARCH AND DEVELOPMENT OF NEW ANTIBIOTICS.

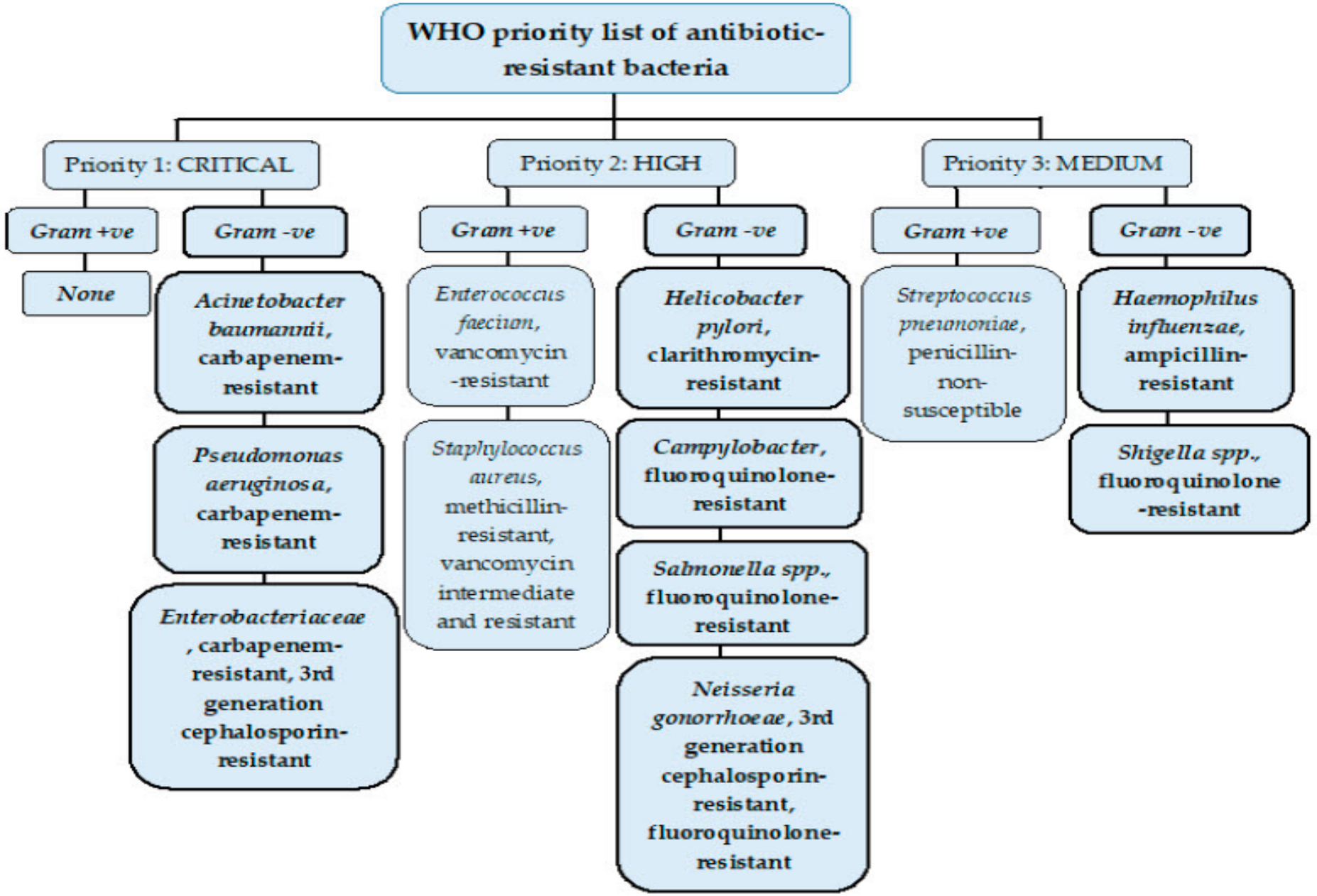
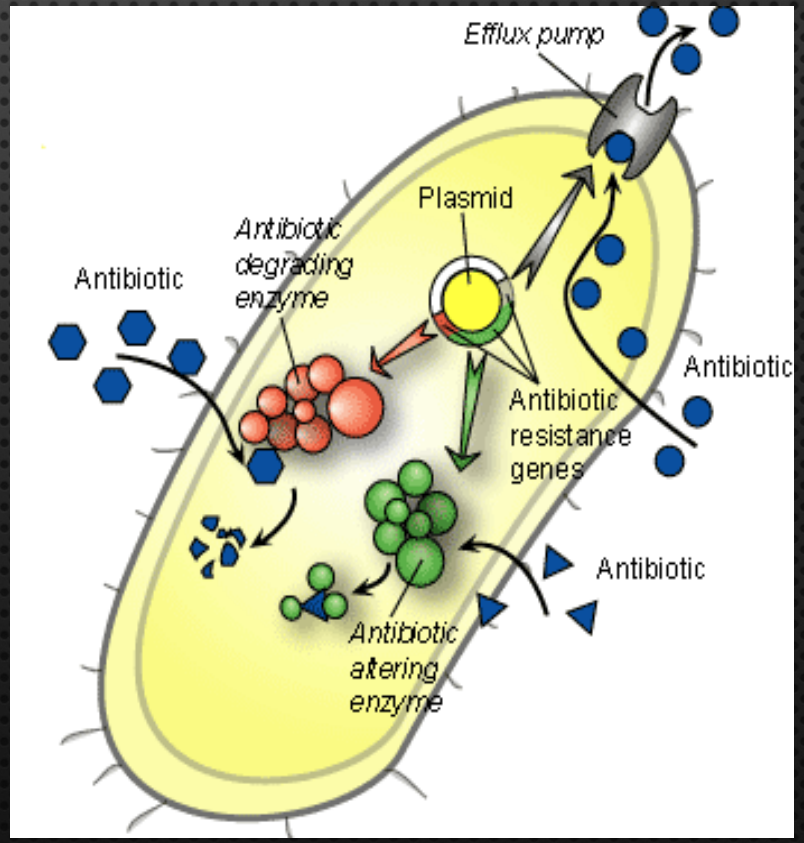


Figure 1. WHO list of priority pathogens grouped under three priority categories according to their antibiotic resistance: Critical, high and medium to encourage research and development of new antibiotics.

MECHANISMS OF ANTIBIOTIC RESISTANCE

- ENZYMATIC DESTRUCTION OF DRUG
- PREVENTION OF PENETRATION OF DRUG
- ALTERATION OF ANTIBIOTIC OR TARGET SITE
- RAPID EJECTION OF THE DRUG



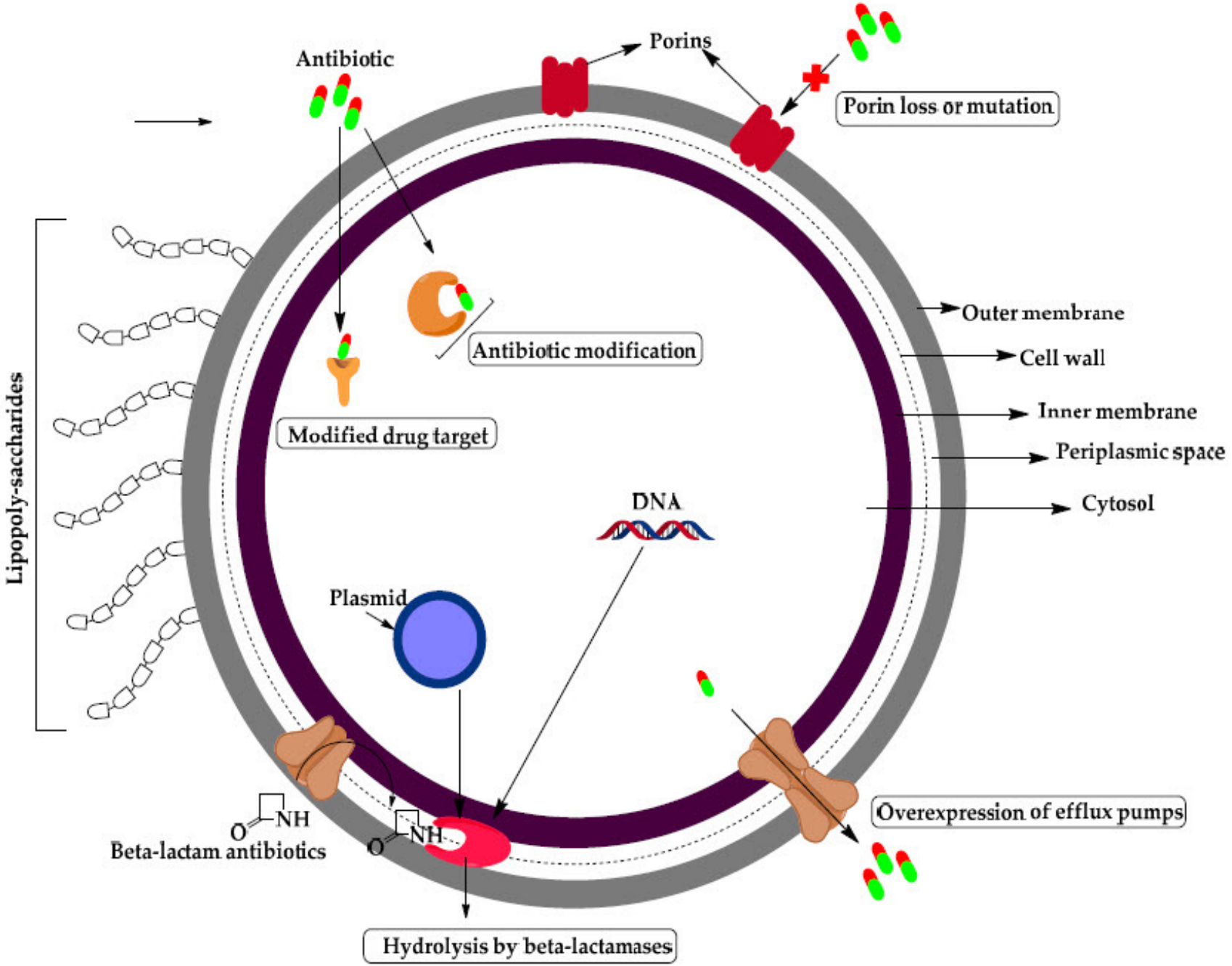
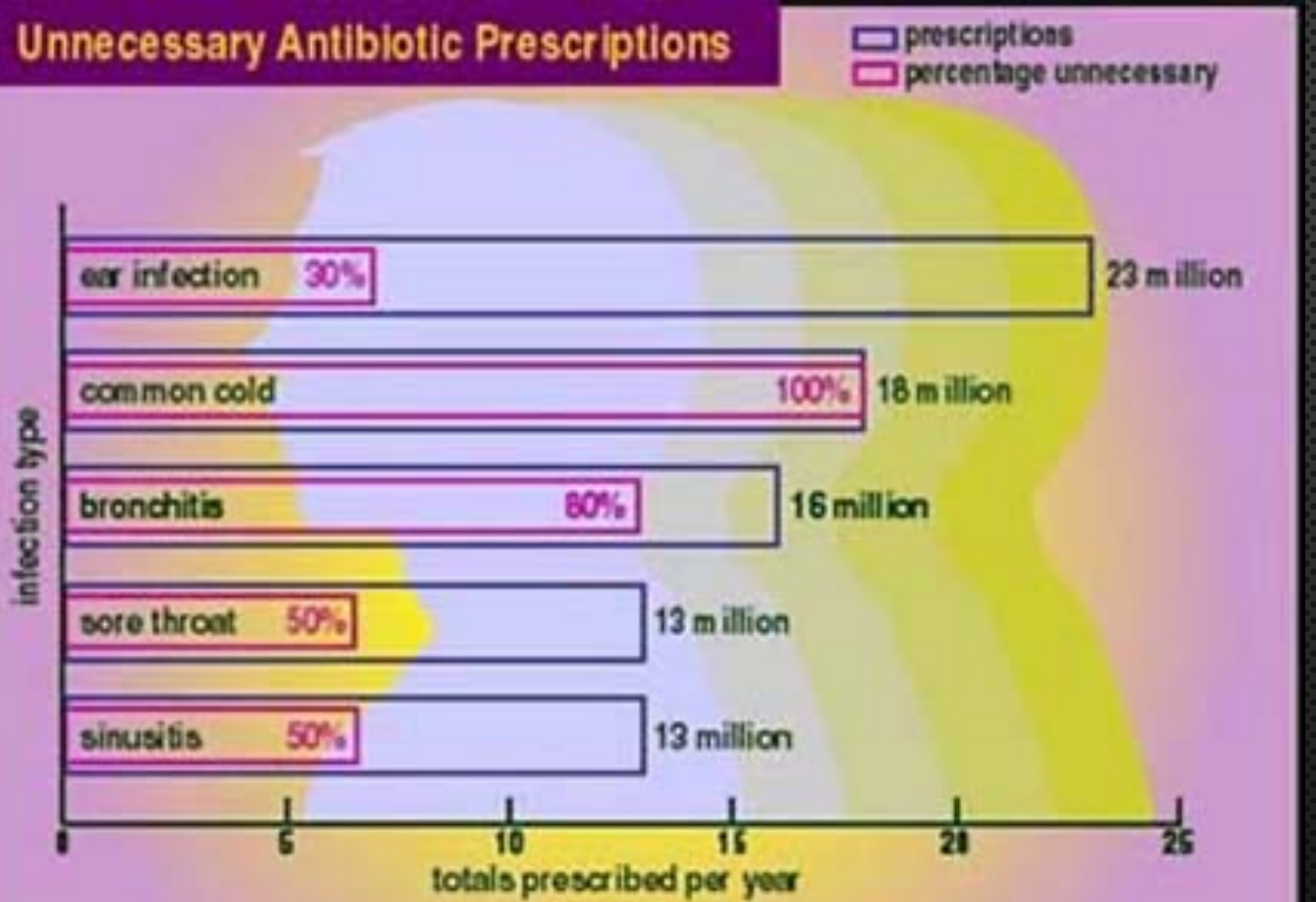


Figure 3. Structure of Gram-negative bacteria and their mechanisms of resistance.

Inappropriate antimicrobial use

- Prescription not taken correctly
- Antibiotics for viral infections
- Antibiotics sold without medical supervision
- Spread of resistant microbes in hospitals due to lack of hygiene

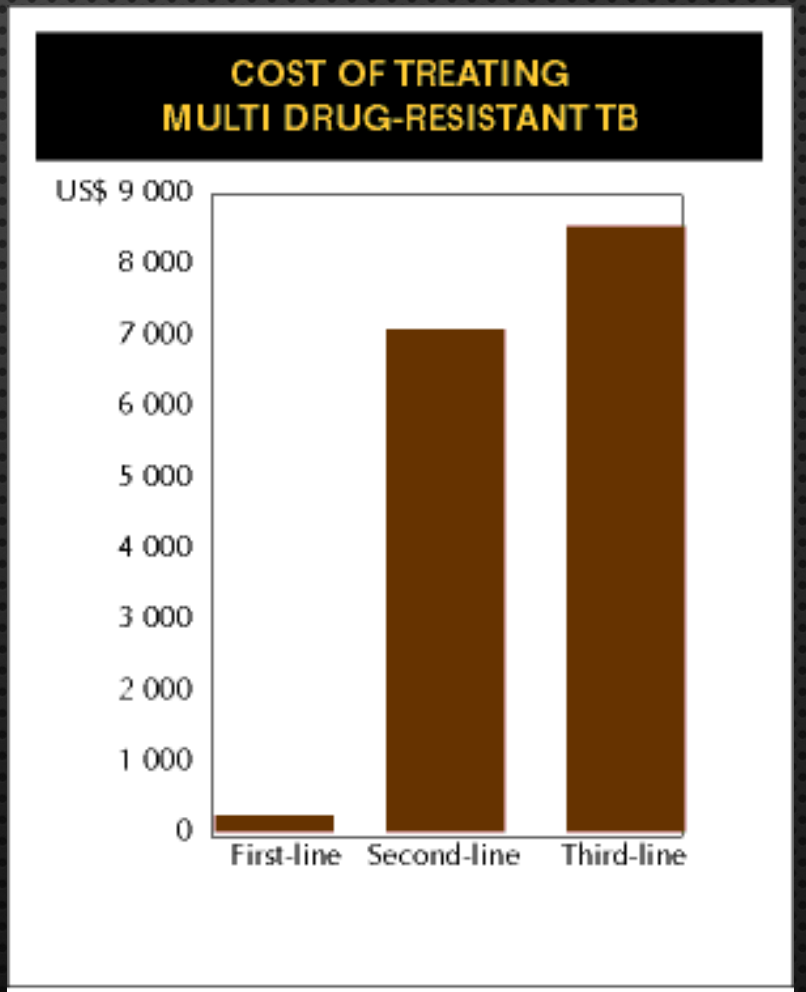
Unnecessary Antibiotic Prescriptions



More than 50 million unnecessary antibiotic prescriptions are written each year for patients outside of hospitals, according to estimates by the Centers for Disease Control and Prevention.

CONSEQUENCES OF ANTIMICROBIAL RESISTANCE

- INFECTIONS RESISTANT TO AVAILABLE ANTIBIOTICS
- COST OF TREATMENT



Source: Farmer et al. The Global Impact of Drug Resistant Tuberculosis, Harvard Medical School and Open Society Institute: pp. 168,1999

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REVIEW

Multidrug-resistant organisms in urinary tract infections in children

Michelle Mahony [1,2] · Brendan McMullan [1,2,3] · Jeremy Brown [4,5] · Sean E Kennedy [1,6]

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DEFINITION

- International consensus now defines multidrug resistance as:
- non-susceptibility to at least one antimicrobial in three or more classes, based on in vitro antibiotic susceptibility testing .
- Extensively drug resistant (XDR) organisms: susceptibility to only one or two antimicrobial classes, with resistance to agents in all remaining categories .
- Pan-drug resistance is resistant to all agents in all antimicrobial classes

MECHANISMS OF RESISTANCE

- MECHANISMS OF ANTIMICROBIAL RESISTANCE IN GRAM-NEGATIVE ORGANISMS .
- THE MOST COMMON MECHANISM IN ENTEROBACTERIALES IS THE PRODUCTION OF BETA LACTAMASES
- ESBL PRODUCERS HYDROLYZE PENICILLINS, FIRST- TO THIRD-GENERATION CEPHALOSPORINS AND AZTREONAM BUT MAY REMAIN SUSCEPTIBLE TO CLAVULANIC ACID COMBINATIONS IN VITRO

Table 1 Ambler classification of selected beta-lactamases

	Enzyme	Example genes	Organisms commonly affected	Notes: implications for detection and treatment
Ambler class A	ESBLs including CTX-M, SHV	$bla_{CTX\text{-}M\text{-}15}$ $bla_{CTX\text{-}M\text{-}27}$ $bla_{CTX\text{-}M\text{-}14}$	*E. coli* *K. pneumoniae* *P. mirabilis*	Inhibited by clavulanic acid Remain susceptible to carbapenems Chromosomal genes may be inducible
	Carbapenemases KPC	*blaKPC*	*E. coli* *K. pneumoniae* *K. oxytoca* *S. marcescens, Enterobacter* spp. *C. freundii*	Inhibited by clavulanic acid
Ambler class B	Metallo-beta-lactamases, including IMP, NDM		*E. coli* *K. pneumoniae* *K. oxytoca* *S. marcescens*, *Enterobacter* spp. *C. freundii*	Remain susceptible to aztreonam NDM producers typically have additional resistance genes
Ambler class C	Cephalosporinases AmpC	$bla_{CMY\text{-}2}$	*Chromosomal AmpC* *Enterobacter* spp. *C. freudii* *S. marcescens* *M. morganii* *P. stuartii* *Plasmid AmpC* *K. pneumoniae* *E. coli*	Chromosomal or plasmid-mediated Chromosomal genes may be inducible Also resistant to aztreonam Remain susceptible to •Carbapenems •4th generation cephalosporins, e.g. cefepime •Avibactam
Ambler class D	Oxacillinases	$bla_{OXA\text{-}23}$ $bla_{OXA\text{-}48}$ $bla_{OXA\text{-}1}$	*A. baumannii* *P. aeruginosa*	Highly diverse group of enzymes, some also hydrolyse carbapenems

Families of beta-lactamase enzymes: *TEM* named after the first patient Temoniera, *SHV* sulphydryl variable, *CTX-M* named as resistance to cefotaxime, *ESBL* extended spectrum beta-lactamases, *KPC Klebsiella pneumoniae* carbapenemase, *MBL* metallo-beta-lactamases, *NDM* New Delhi metallo-beta-lactamase [3, 5, 10]

Table 2 Non-beta-lactamase mechanisms of antibiotic resistance in Gram-negative organisms

Antibiotic class	Mechanism of resistance	Organisms
Aminoglycosides	Target site mutation—production of 16S rRNA methylases	*E. coli* *K. pneumoniae* *P. aeruginosa* *Acinetobacter* spp.
	Drug modification—production of aminoglycoside-modifying enzymes Phosphotransferases (APH) Acetyltransferases (AAC) Nucleotidyltransferases (ANT)	*E. coli* *K. pneumoniae* *A. baumannii* *P. aeruginosa*
Quinolones	Target site mutation—DNA gyrase and topoisomerase IV	*E. coli* *Klebsiella* spp. *P. aeruginosa*
	Pentapeptide repeats—Qnr	*E. coli* *Klebsiella* spp.
Trimethoprim or trimethoprim-sulfamethoxazole	Overproduction of enzymes Dihydropteroate synthase (DHPS) Dihydrofolate reductase (DHFS)	*E. coli*

This table provides common/important examples rather than a comprehensive list [3, 5, 10]

RISK FACTORS FOR COLONIZATION WITH MDROS

- Colonization, which may precede infection, refers to the presence of bacteria (MDROs or otherwise), in the human body, which are not causing disease.
- colonization may persist for up to 4 years and perhaps longer
- In a prospective study of French children, history of hospitalization within the last 6 months
- international travel history.
- recent use of oral third-generation cephalosporins
- Asian ethnicity and gastrointestinal comorbidities.
- hospitalized neonates include prolonged mechanical ventilation, prolonged hospital stay, use of invasive devices and antibiotic use .
- Younger gestational age and low birth weight.

RISK FACTORS FOR MDR UTI

THE MOST FREQUENTLY RISK FACTORS ARE:

- PREVIOUS ANTIBIOTIC USE
- URINARY TRACT ANOMALIES
- PREVIOUS HOSPITALIZATION
- COMMUNITY-ACQUIRED MDRO INFECTION MAY OCCUR IN CHILDREN WITHOUT ANY IDENTIFIABLE RISK FACTOR
- NON-GENITOURINARY ANOMALIES; MALIGNANCY, SEPSIS, DIABETES MELLITUS, GASTROINTESTINAL ANOMALIES, DEVELOPMENTAL DELAY AND INHERITED DISORDERS OF METABOLISM

Risk factors for MDR UTI

- Recent antibiotic use, including both therapy and prophylaxis
- The presence of underlying genitourinary anomalies is associated with both recurrent UTIs and increased risk of MDRO.
- Urinary tract anomalies include VUR, hydronephrosis, dysplastic kidney, nephrolithiasis, bladder augmentation and Mitrofanoff procedures and other anatomical and functional anomalies
- clean intermittent catheterization (CIC)
- Functional bladder bowel dysfunction (BBD)
- Previous hospitalization within the last 3 months

GLOBAL PREVALENCE OF MDRO COLONIZATION AND UTI IN CHILDREN

Table 3 Prevalence of ESBL-producing organisms causing UTI in children

Author Year Country	*N* Age range	Organisms	Proportion with ESBL as percentage
Ahmed et al. [35]	84	*E. coli*	48.8
2015	6 months–5 years	*K. pneumoniae*	
Tanzania		Other	
Degnan et al. [36]	370	Total Gram-negative	7.8
2015	0–18 years	*E. coli*	9.3
USA		*K. pneumoniae*	24.7
		K. oxytoca	35.3
Fan et al. [24]	312	*E. coli*	33.3
2014	0–15 years		
Taiwan			
Logan et al. [14]	363,398[a]	*E. coli*	0.5
2014	1–17 years	*K. pneumoniae*	
USA		*P. mirabilis*	
Parajuli et al. [37]	739	*E. coli*	38.9
2017	0–14 years		
Nepal			
Perez Haras et al. [34]	229	*E. coli*	9.2
2017	0–14 years		
Spain			
Rezai et al. [38]	327	*E. coli*	30.5
2015	Not stated		
Iran			
Sharma et al [39]	75	*E. coli*	48.0
2016	0–10 years		
India			
Topaloglu et al. [25]	4105	Gram-negative	3.8
2010	Not stated		
Turkey			
Yun et al. [40]	114	*E. coli*	14.0
2017	0–18 years		
South Korea			
Zerr et al. [28]	1204	Gram-negative	17.4
2016	0–21 years		
USA			

[a] Note only 62.11% of these from urinary sources

GLOBAL PREVALENCE OF MDRO COLONIZATION AND UTI IN CHILDREN

Table 4 Prevalence of MDR and XDR UTIs in children

Author Year Country	*N* Age range	Organisms	Proportion with MDR as percentage	Proportion with XDR as percentage
Raman et al. [26] 2018 Australia	2202 *E. coli* 1676 0–18 years	Gram-negative organisms *E. coli*	14.0 8.3	Not stated
Lagace-Wiens et al. [41] 2011 Canada	3789 total; subgroup 0–18 years (*N* not stated)	*E. coli*	11.6 in 0–18 year subgroup	Not stated
Sharma et al. [39] 2016 India	75 0–10 years	*E. coli*	90.0	Not stated
Yun et al. [40] 2017 South Korea	114 0–18 years	*E. coli*	26.3	Not stated
Parajuli et al. [37] 2017 Nepal	739 0–14 years	*E. coli*	64.0	5.0
Perez Haras et al. [34] 2017 Spain	229 0–14 years	*E. coli*	5.0	Not stated
Bryce et al. [42] 2018 UK	41 0–5 years	*E. coli*	17.1	Not stated

OUTCOME

- MDRO UTI can lead to delayed initiation of appropriate therapy and poorer outcomes
- Community-acquired ESBL infections have more frequent early treatment failure
- frequent complications and increased mortality
- increased length of stay, ICU admissions and a trend towards a higher mortality rate