

نوزدهمین همایش سالیانه
انجمن پزشکان عفونی کودکان ایران
و پانزدهمین بزرگداشت
استاد دکتر سید احمد سیادتی

Antibacterial therapy in infections caused by Gram-Negative Bacteria

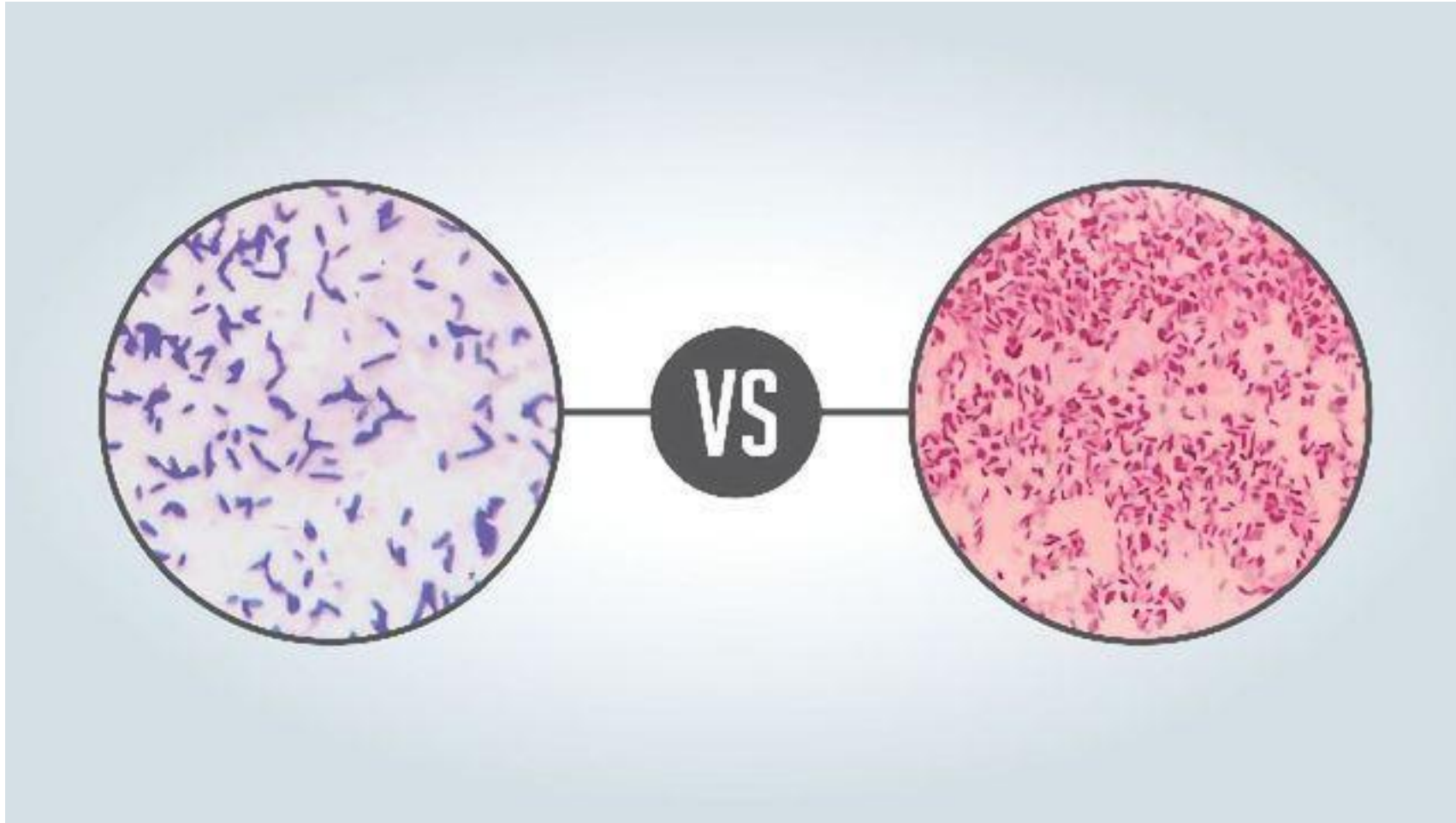


Gholamreza Pouladfar MD

Subspecialty of pediatric infectious diseases
Shiraz University of medical Sciences

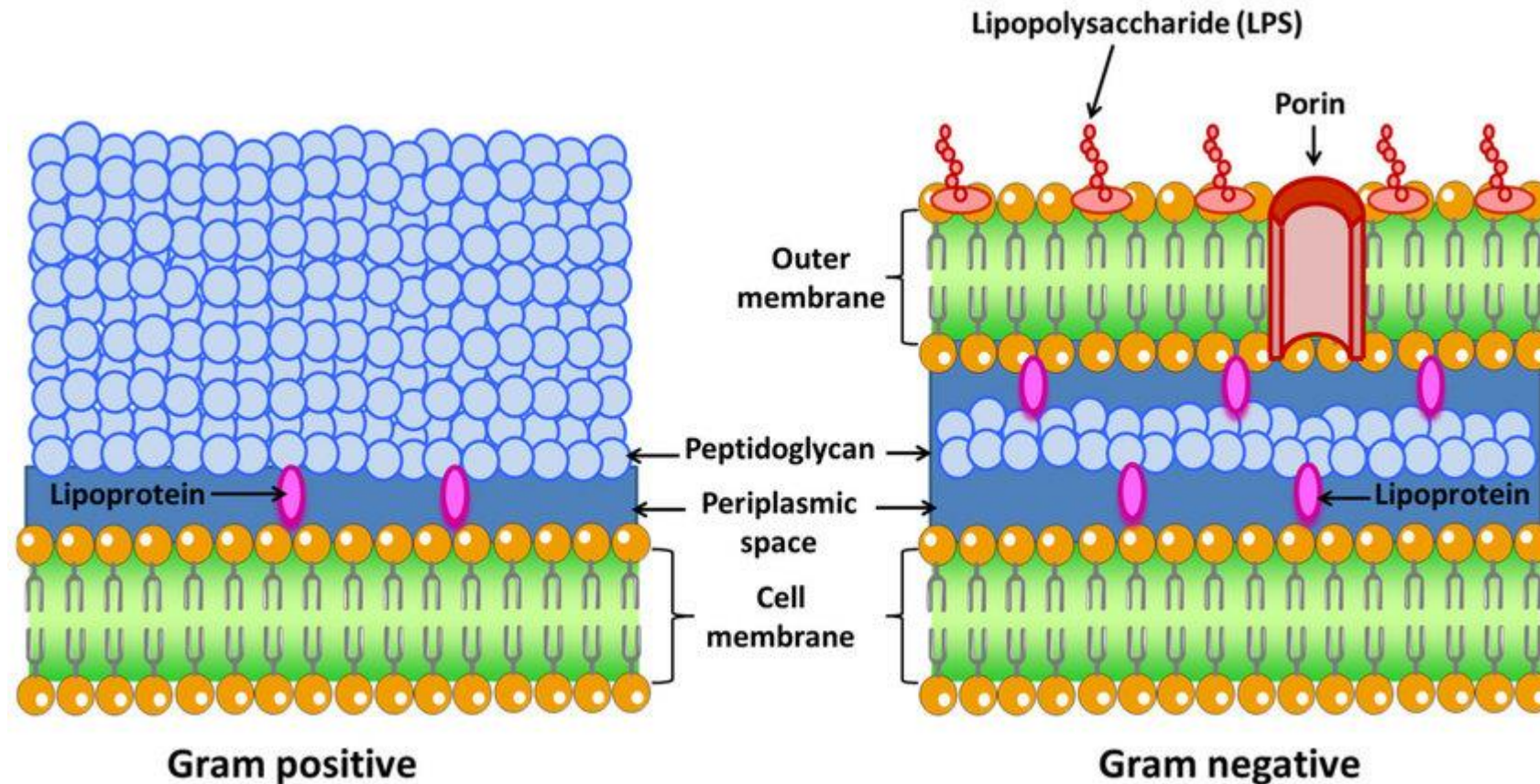
2023



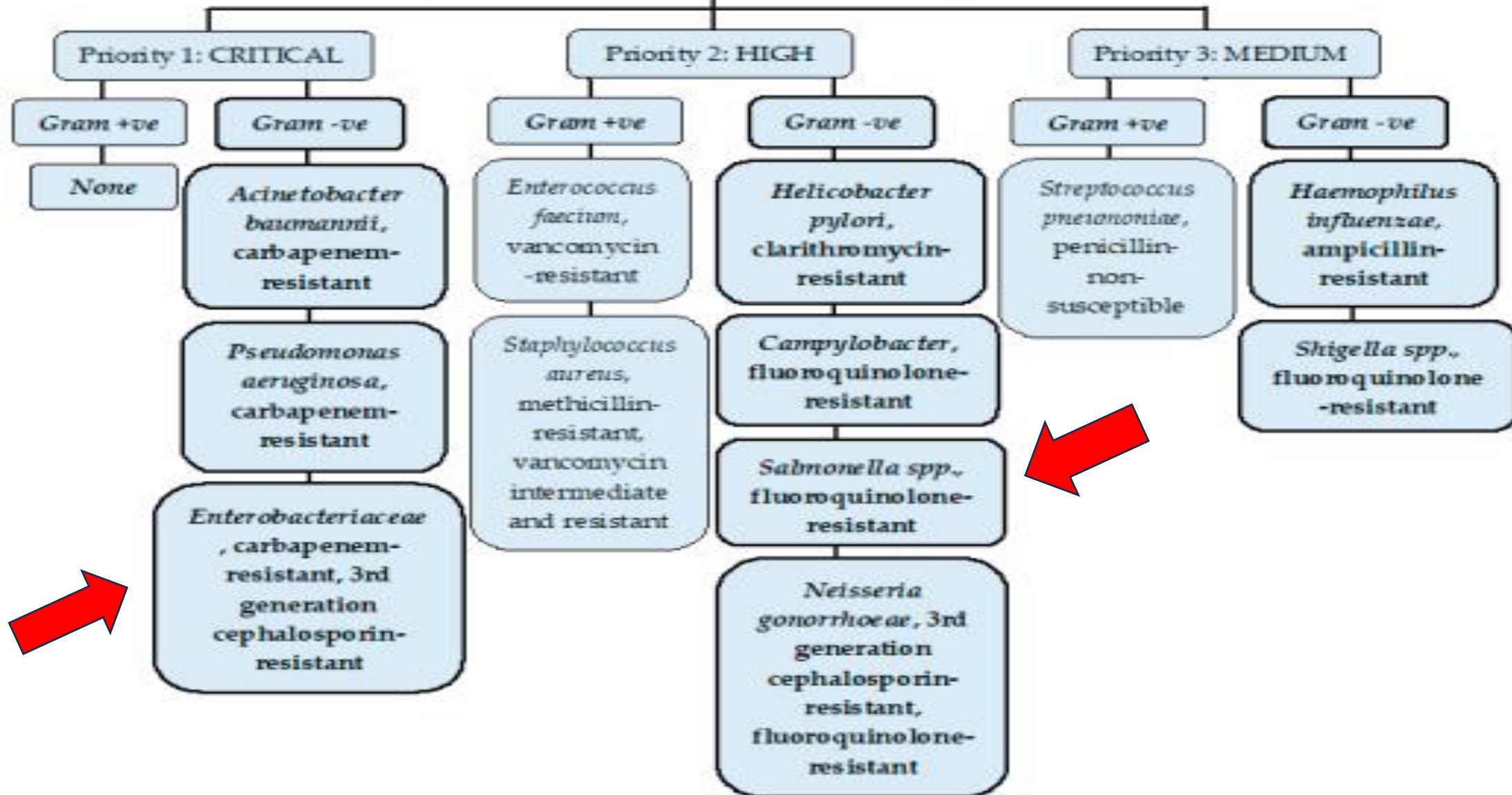


In 1884 **Hans Christian Gram** developed a method to distinguish between Gram-positive and Gram- negative bacteria

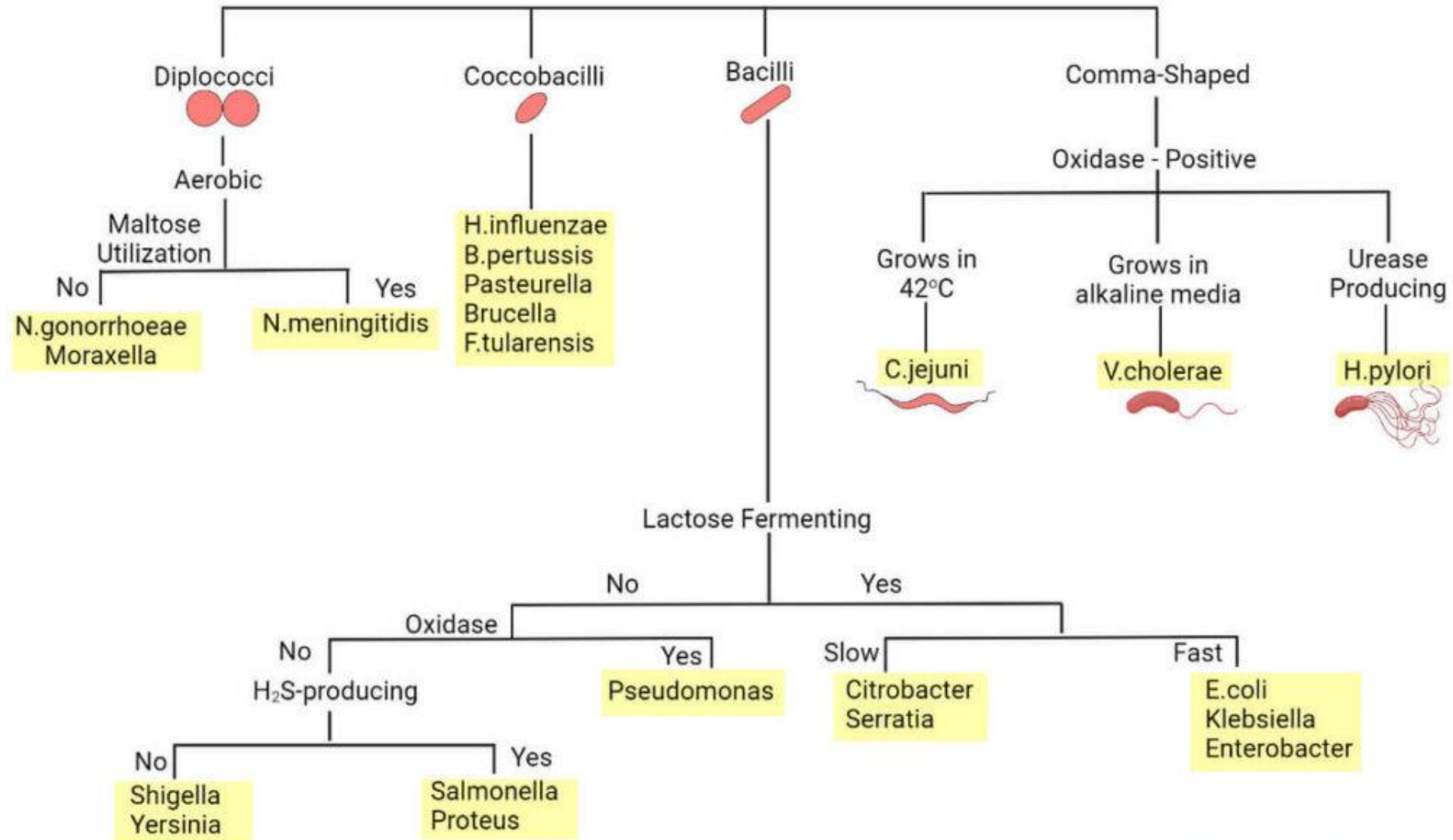
Differences between Gram-negative and Gram-positive bacteria.



WHO priority list of antibiotic-resistant bacteria

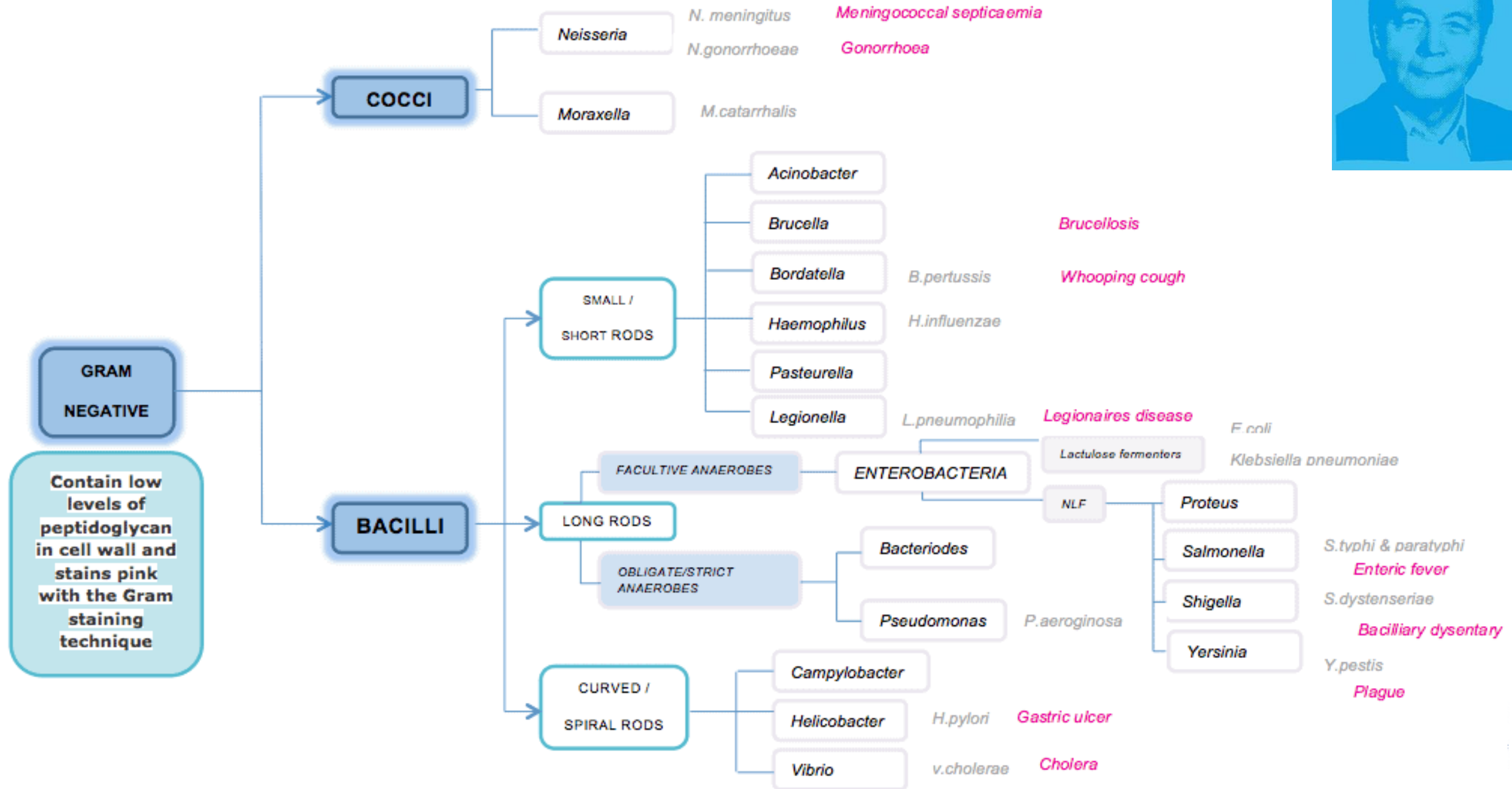
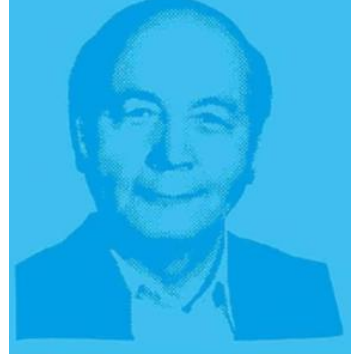


Gram-Negative Bacteria



LaboratoryInfo







Neisseria meningitidis

- A gram-negative diplococcus
- 12 confirmed serogroups based on capsular type
- Invasive meningococcal infection
 - 1) Septicemia (35%–40% of cases)
 - 2) Meningitis (~50% of cases), or both.
 - 3) Bacteremic pneumonia is less common (10% of cases).



Neisseria meningitidis

- Treatment options:
 - cefotaxime, ceftriaxone
 - Penicillin G
 - Ampicillin.
- β -lactamase-producing organisms
 - Empirical therapy: **cefotaxime or ceftriaxone.**
- 5 to 7 days
- A life-threatening penicillin allergy characterized by anaphylaxis:
 - 1) **Meropenem**
 - 2) Cross-reactivity in penicillin-allergic adults is very low



Haemophilus influenzae

- Gram-negative, coccobacilli
- Facultatively anaerobic
- Two types based on its polysaccharide:
 - (1) capsulated with six serotypes from a to f
 - (2) non-capsulated [28].

- Pneumonia
- Meningitis
- Bacteremia



type b strain H. influenzae

- community-acquired pneumonia
- AOM
- Sinusitis



commonly caused by
a non-capsulated form



Amoxicillin

the main treatment against H. influenza

- The mechanism of resistance
 - 1) β - lactamases (TEM-1 or ROB-1)
 - 2) PBP target modifications (point mutations in the *ftsI* gene)
- 1) β -lactamase negative, ampicillin-sensitive (BLNAS) strains
- 2) β -lactamase positive, ampicillin-resistant (**BLPAR**) strains
- 3) BLNAR strains
- 4) β -lactamase-producing **amoxicillin/clavulanic acid-resistant** (BLPACR) strains.



✓ amoxicillin-clavulanate

✓ cefuroxime



Bordetella pertussis

Pertussis

- A fastidious, gram-negative, pleomorphic bacilli
- the catarrhal stage
- Azithromycin
 - First-line choice
 - 5 day
 - for treatment and for postexposure prophylaxis



Bordetella pertussis

Pertussis

- Resistance to macrolide antimicrobial agents: rarely
- Penicillins and first- and second-generation cephalosporins are not effective.
- infantile hypertrophic pyloric stenosis (IHPS)
- in the first 6 weeks of life



Bordetella pertussis

Trimethoprim-sulfamethoxazole

- An alternative
-
- Limitation: use in **> 2-month** infants and children
- Indications:
 - 1) cannot tolerate macrolides
 - 2) are infected with a macrolide-resistant strain
- Limited studies



Bordetella pertussis

Age	Recommended Drugs			Alternative
	Azithromycin	Erythromycin	Clarithromycin	TMP-SMX
Younger than 1 mo	10 mg/kg/day as a single dose daily for 5 days ^{b,c}	40 mg/kg/day in 4 divided doses for 14 days	Not recommended	Contraindicated at younger than 2 mo
1 through 5 mo	10 mg/kg/day as a single dose daily for 5 days ^b	40 mg/kg/day in 4 divided doses for 14 days	15 mg/kg/day in 2 divided doses for 7 days	2 mo or older: TMP, 8 mg/kg/day; SMX, 40 mg/kg/day in 2 doses for 14 days
6 mo or older and children	10 mg/kg as a single dose on day 1 (maximum 500 mg), then 5 mg/kg/day as a single dose on days 2 through 5 (maximum 250 mg/day) ^{b,d}	40 mg/kg/day in 4 divided doses for 7–14 days (maximum 2 g/day)	15 mg/kg/day in 2 divided doses for 7 days (maximum 1 g/day)	2 mo or older: TMP, 8 mg/kg/day; SMX, 40 mg/kg/day in 2 doses for 14 days
Adolescents and adults	500 mg as a single dose on day 1, then 250 mg as a single dose on days 2 through 5 ^{b,d}	2 g/day in 4 divided doses for 7–14 days	1 g/day in 2 divided doses for 7 days	TMP, 320 mg/day; SMX, 1600 mg/day in 2 divided doses for 14 days



Azithromycin

should be used with caution in people
with

prolonged QT interval

and certain proarrhythmic conditions.



Enterobacteriaceae

- Escherichia coli
- Klebsiell spp.
- Enterobacter spp.

- UTIs
- Blood-stream infections
- Hospital, and healthcare-associated pneumonia.

- Resistance :
 - the production of ESBLs (the main mechanism)



Enterobacteriaceae- 3rd Generation Cephalosporin-Resistant

- The production of β -lactamases
- ESBLs
 - hydrolyze broad-spectrum cephalosporins, monobactams, and penicillins.



treatment of Enterobacteriaceae infections caused by ESBL-producing organisms

- A carbapenem
 - The choice
 - especially certain K pneumoniae isolates.
- Of the aminoglycosides
 - amikacin retains the most activity against ESBL-producing strains.



Carbapenemase-producing Enterobacteriaceae

- 1) *Klebsiella pneumoniae*, *E coli*, and *Enterobacter cloacae*
- 2) ESBL- and carbapenemaseproducing bacteria
- 3) often carry additional plasmid-borne genes
 - 1) High-level resistance to
 - 1) Aminoglycosides
 - 2) Fluoroquinolones
 - 3) trimethoprim-sulfamethoxazole.



What are preferred antibiotics for the treatment of uncomplicated cystitis caused by ESBL-E?

- **Nitrofurantoin and TMP-SMX** are preferred treatment options for uncomplicated cystitis caused by ESBL-E.
- **Ciprofloxacin, levofloxacin, and carbapenems** are alternative agents for uncomplicated cystitis caused by ESBL-E.
- Treatment with a single intravenous (IV) dose of an **aminoglycoside** is an alternative treatment option for uncomplicated ESBL-E cystitis



Fluoroquinolones

an increased risk for

- 1) prolonged QTc intervals
- 2) tendinitis and tendon rupture
- 3) aortic dissections
- 4) Seizures
- 5) peripheral neuropathy
- 6) Clostridioides difficile infections



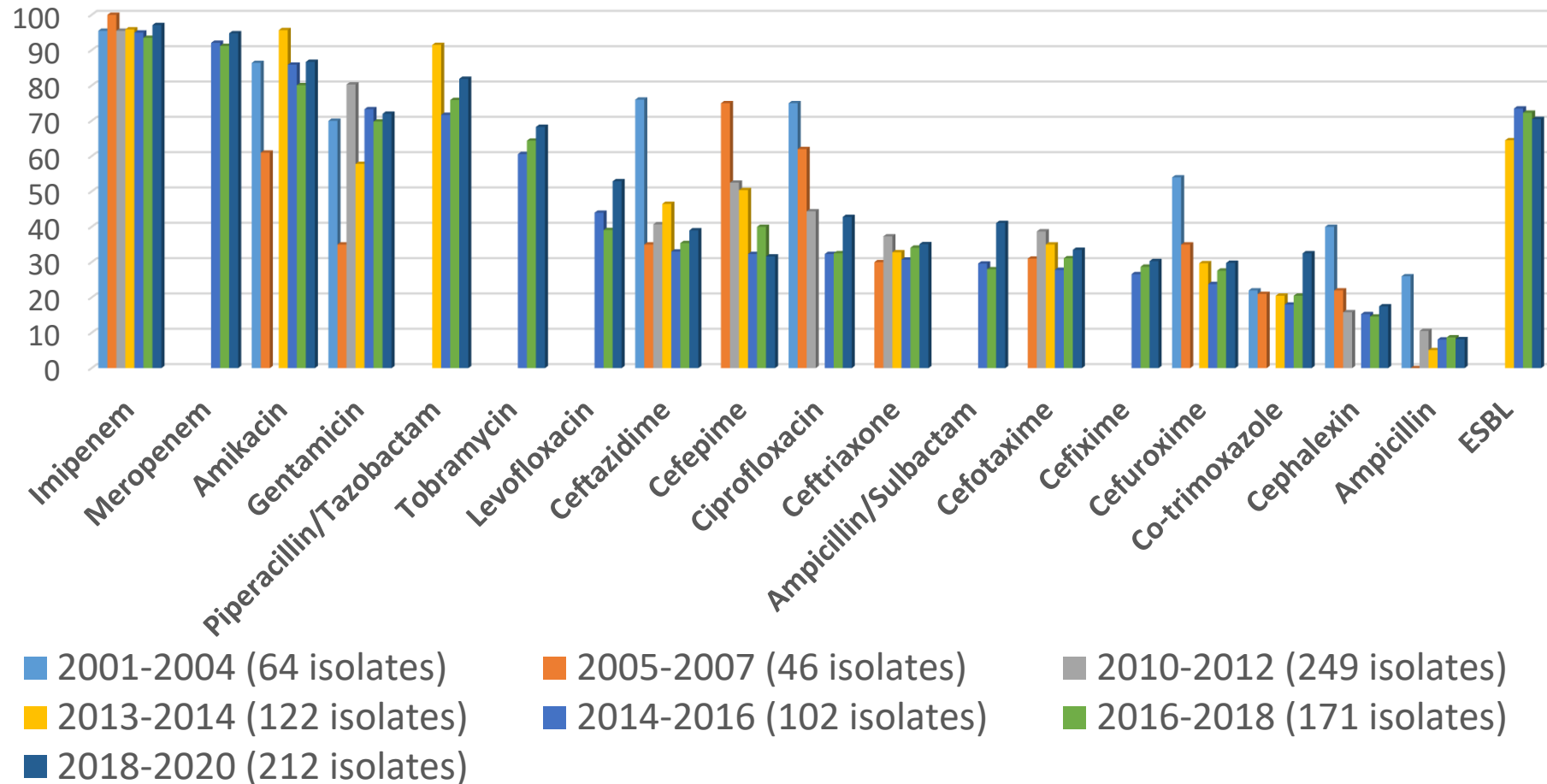
What are preferred antibiotics for the treatment of pyelonephritis and cUTI caused by ESBL-E

IDSA, 2023

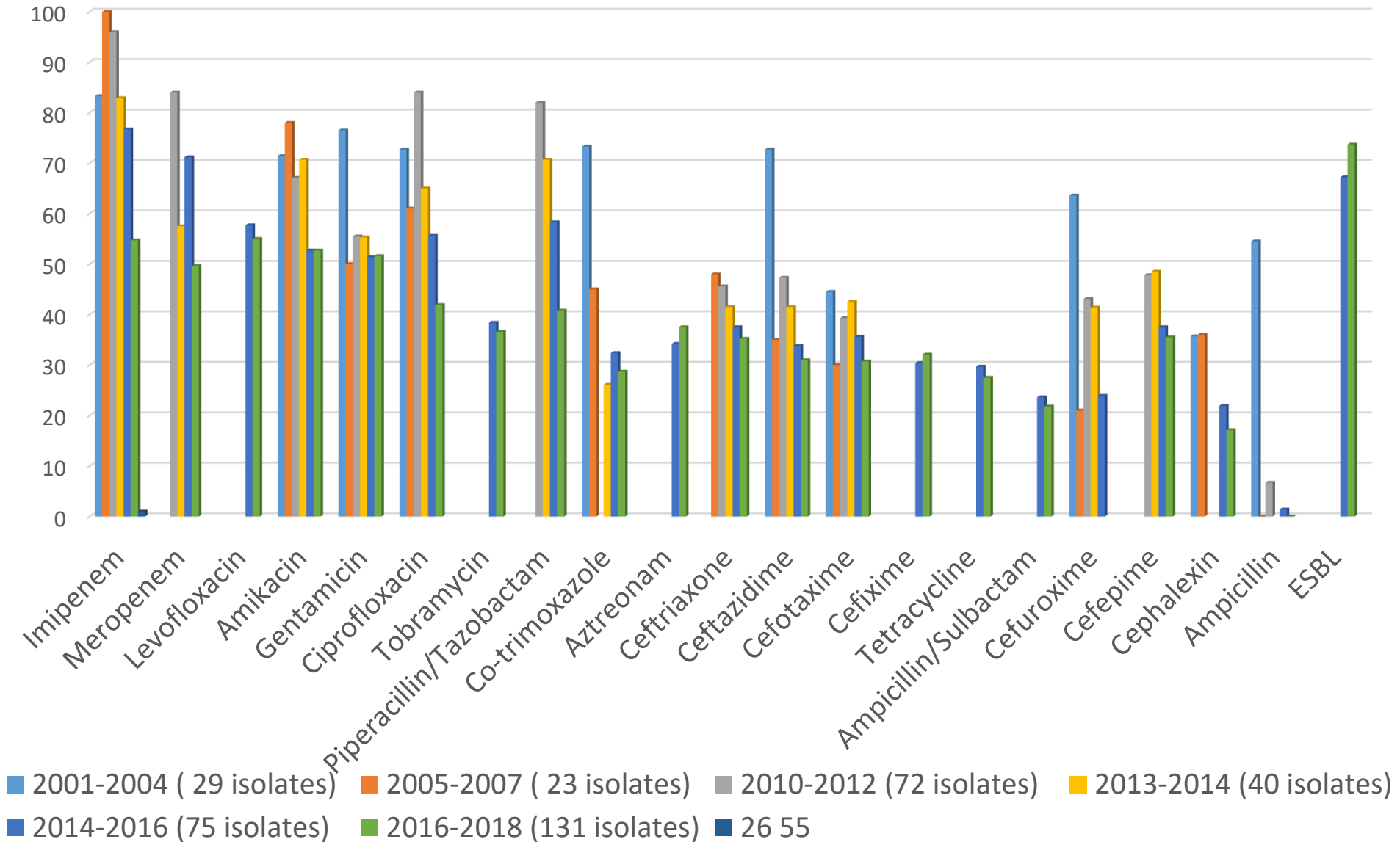
- **TMP-SMX, ciprofloxacin, or levofloxacin**
 - are preferred treatment options.
- **Ertapenem, meropenem, and imipenem-cilastatin**
 - are preferred agents when **resistance or toxicities** preclude the use of TMP-SMX or fluoroquinolones.
- **Aminoglycosides** for a full treatment course
 - are an **alternative** option



Rates of Sensitivity to Different Antibiotics Tested against 924 *Escherichia coli* Strains Isolated from Bloodstream Infections, in Seven Episodes, Shiraz, Iran

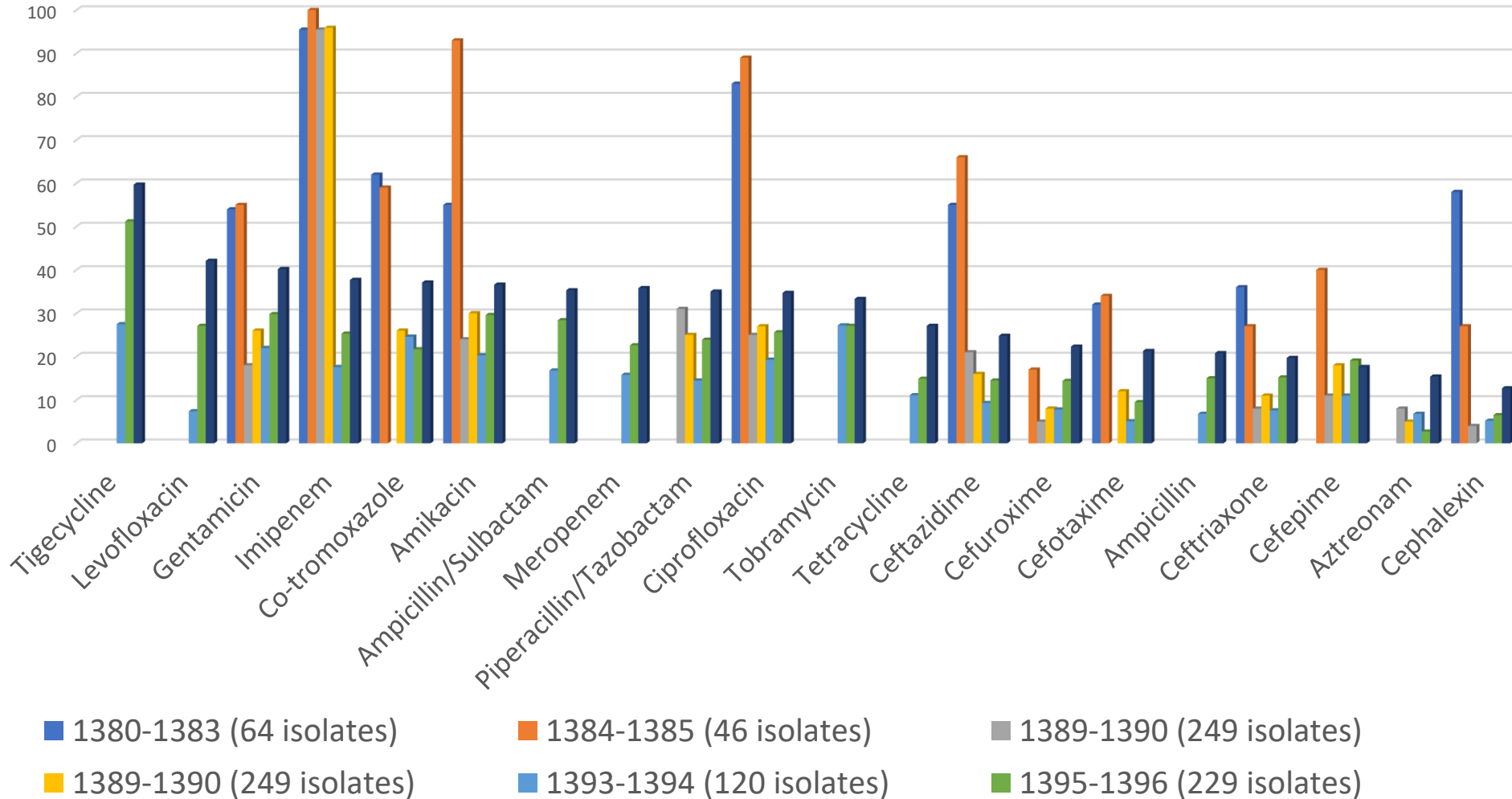


Rates of Sensitivity to Different Antibiotics against *539 Klebsiella spp.* Strains Isolated from Bloodstream Infections, in Seven Episodes, Shiraz, Iran



2018-2020

Rates of Sensitivity to Different Antibiotics Tested against **1084 Strains of *Acinetobacter* Species** Isolated from Bloodstream Infections, in Seven Episodes, Shiraz, Iran



Shigella species

- facultative aerobic, gram-negative bacilli
- The family Enterobacteriaceae.
- Four species
 - 1) *Shigella sonnei* : most common in the United States.
 - 2) *Shigella flexneri*:
 - 3) *S dysenteriae*
 - 4) *Shigella boydii*.



Antimicrobial therapy in shigellosis

Treatment options:

- 1) Oral cephalosporins (eg, cefixime): Unclear efficacy
- 2) Parenteral ceftriaxone for 2 to 5 days.
- 3) A fluoroquinolone (eg, ciprofloxacin) for 3 days.
- 4) Azithromycin for 3 days
- 5) Oral ampicillin or trimethoprim-sulfamethoxazole for 5 days
 - For susceptible strains,

Shortening
duration of
diarrhea

Hastening
eradication of
organisms



Shigella resistance situation in IRAN

In 233 stool sample, The resistance rate of Shigella spp. to

- Azithromycin, 25.5%
- Ceftriaxone, 43.6%
- **Ciprofloxacin, 3.8%**
- **co-trimoxazole, 82.9%**
- **Nalidixic acid, 15.9%**
- Gentamicin, 26.6%
- Amoxicillin, 40.4%
- **Ampicillin, 57.4%**
- Doxycycline , 41.4%
- **Cefixime , 22.3%**
-

Journal Infect Chemother. 2020
Sep;26(9):955-958. North east of Iran



Enteric Fever.

Salmonella enterica serovars

- 1) S. Typhi, Paratyphi A, Paratyphi B, and Paratyphi C
- 2) Restricted to human hosts
- 3) can cause a protracted bacteremic illness
- 4) Clinical and subclinical infections



Nontyphoidal Salmonella (NTS) Infections

- Salmonella Typhimurium, S. Enteritidis, S. I:4,[5],12:i:- , S. Dublin
- A **spectrum of illness** ranging from
 - 1) Asymptomatic gastrointestinal tract carriage
 - 2) Gastroenteritis
 - 3) UTI
 - 4) Bacteremia
 - 5) Focal infections
 - 1) Meningitis
 - 2) Brain abscess
 - 3) Osteomyelitis (to which people with sickle cell anemia are predisposed).



Treatment of NTS Infection.

- Antimicrobial therapy usually is **not indicated** for patients with either
 1. asymptomatic infection **or**
 2. uncomplicated gastroenteritis
 - 1) therapy does **not shorten** the duration of diarrheal disease
 - 2) can prolong duration of **fecal shedding**
 - 3) increases symptomatic **relapse rate**.



Indications for treatment of NTS: Gastroenteritis

- 1) Infants younger than 3 months
- 2) Chronic gastrointestinal tract disease
- 3) Malignant neoplasms
- 4) Hemoglobinopathies
- 5) HIV infection & Other immunosuppressive illnesses or therapies.
- 6) Severe symptoms such as severe diarrhea or prolonged or high fever

People at
increased risk for
invasive disease



Treatment of NTS: Gastroenteritis

Two options:

- (1) an initial dose of **ceftriaxone** then oral **azithromycin**
 - The patient who does **not appear ill** or have evidence of disseminated infection
- (2) A fluoroquinolone
 - an alternative option
- a total 7- to 10-day course



Treatment of NTS: Gastroenteritis

- **Ciprofloxacin non-susceptible strains**
 - increased from 2% in 2009 to 8% in 2017 (US)
- **Extensively drug-resistant (XDR) S Typhi**
 - 2016, in Pakistan
 - An ongoing large epidemic
- Resistance to
 - 1) Ceftriaxone
 - 2) Ampicillin
 - 3) Ciprofloxacin
 - 4) TMP-SMX
- Susceptible only to **azithromycin and carbapenems**



Enteric fever caused by S Typhi

- Empiric therapy with
 - 1) a parenteral third-generation cephalosporin **or**
 - 2) azithromycin
- A least **7 to 10 days** for people with uncomplicated disease
- a 14-day course of therapy (Culture result)
 - amoxicillin or TMP-SMX





نوزدهمین همایش سالیانه
انجمن پزشکان عفونی کودکان ایران
و پانزدهمین بزرگداشت
استاد دکتر سید احمد سیادت



16th

Professor Alborzi
International
Congress of Clinical
Microbiology

محور کنگره:

فوریت های بیماری های عفونی
و نقش آزمایشگاه

Congress Theme:

The Infectious Diseases
Emergencies and
the Role of Laboratory



12-14 December 2023 | Shiraz, Iran

۲۱ تا ۲۳ آذرماه ۱۴۰۲، شیراز

<https://paiccm2023.sums.ac.ir>

Professor_Alborzi_cmrc

alborzicmrc20@gmail.com

۰۷۱-۳۶۴۷۴۳۰۴

