Kurdistan University of Medical Sciences

Antibiotic Resistances Profile in Iran, Clinical Implication and Prospect for Antibiotic Stewardship

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2 Surveillance of Antibiotic resistances

- Knowledge of the prevalence of antibiotic resistance is a pre-requisite for infection control and essential for public healthcare policy makers to conduct effective responses. Currently, a well-organized nationwide surveillance system is only present in three countries/regions, namely USA, European Union and Thailand.
- A nationwide surveillance system has not yet been established in Iran. Most of the information about antibiotics resistance is retrieved from cross sectional studies.

Frequencies of isolates obtained from positive blood cultures (cross sectional studies-Iran)								
	Pouladfar, et al; 2013-2014 Shiraz (1)		Pourabbas, et al; 2010-2011, Iran(2)		Soltani, et al; Sanandaj, 2016		Total (sum)	
Isolated Bacteria	No.	%	No.	%	No.	%	No.	%
Coagulase-negative staphylococci	562	35.52%	---	---	5	4.27%	567	22.17%
Coagulase-positive staphylococci	125	7.90%	224	26.11%	29	24.79%	378	14.78%
Escherichia coli	122	7.71%	146	17.02%	32	27.35%	300	11.73%
Pseudomonas spp	109	6.89%	95	11.07%	3	2.56%	207	8.10%
Acinetobacter spp	95	6.01%	67	7.81%	7	5.98%	169	6.61%
Klebsiella spp	78	4.93%	148	17.25%	3	2.56%	229	8.96%
Candida spp	75	4.74%	---	---	---	---	75	2.93%
Vancomycin Resistance Entrococcus	60	3.79%	---	---	---	---	60	2.35%
Streptococcus spp	55	3.48%	---	---	---	---	55	2.15%
Entrococcus spp	47	2.97%	---	---	1	0.1%	48	1.88%
Other	37	2.34%	---	---	---		37	1.45%
Entrobacter spp	32	2.02%	38	4.43%	9	7.69%	79	3.09%
Bacillus spp	22	1.39%	---	---	---	---	22	0.86%
Stenotrophomonas maltophilia	20	1.26%	35	4.08%	25	21.37%	80	3.13%
Serratia spp	17	1.07%	105	12.24%	2	1.71%	124	4.85%
Brucella spp	10	0.63%	---	---	---	---	10	0.39%
Proteous spp	6	0.38%	---	---	---	---	6	0.23%
Streptococcus pneumoniae	6	0.38%	---	---	---	---	6	0.23%
Salmonella spp	5	0.32%	---	---	---	---	5	0.20%
Citrobacter spp	2	0.13%	---	---	---	---	2	0.08%
Shigella	---	---	---	---	1	0.1%	1	0.04%
Total	1485	---	858	---	117	---	2460	100.00%

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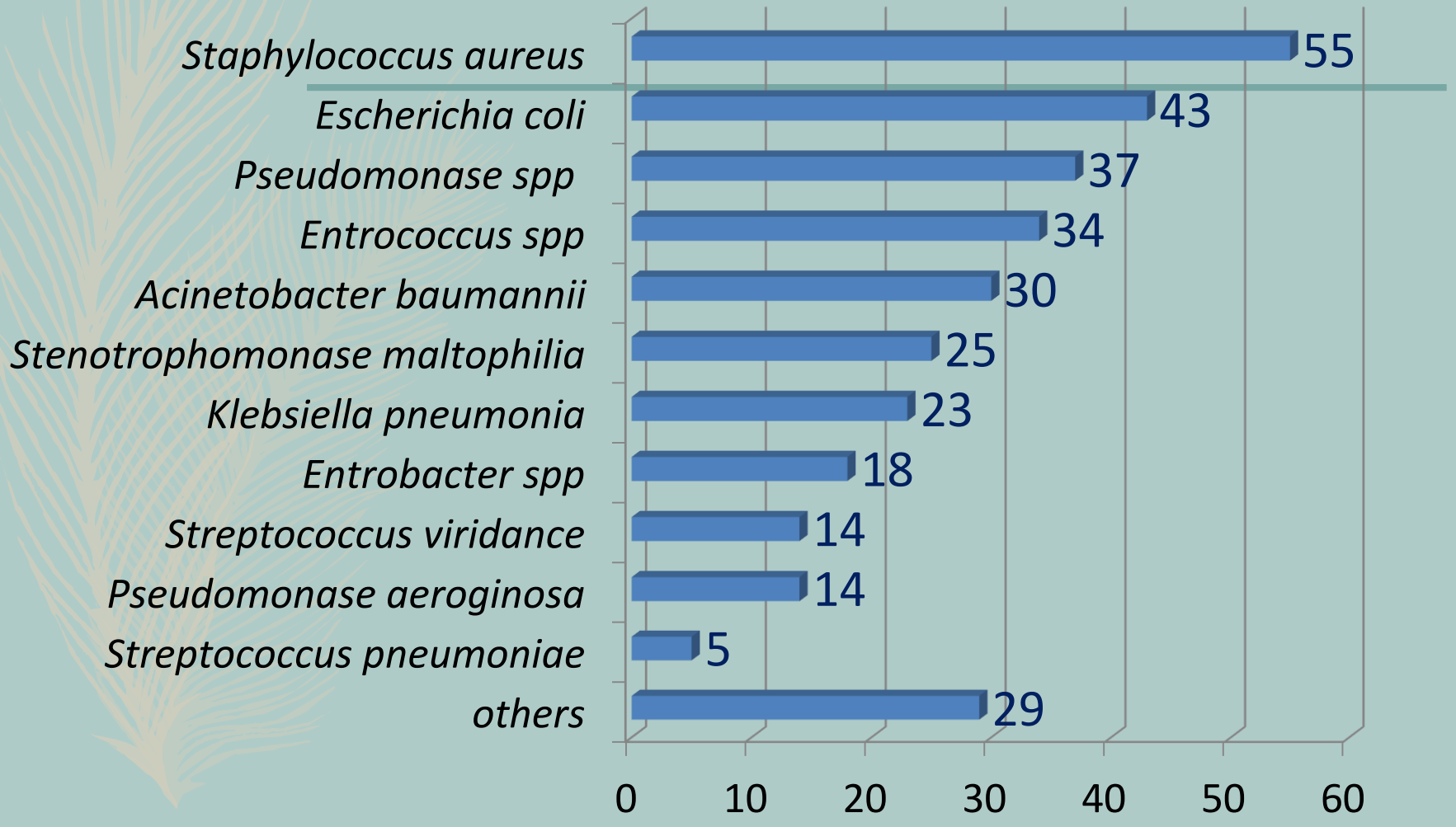
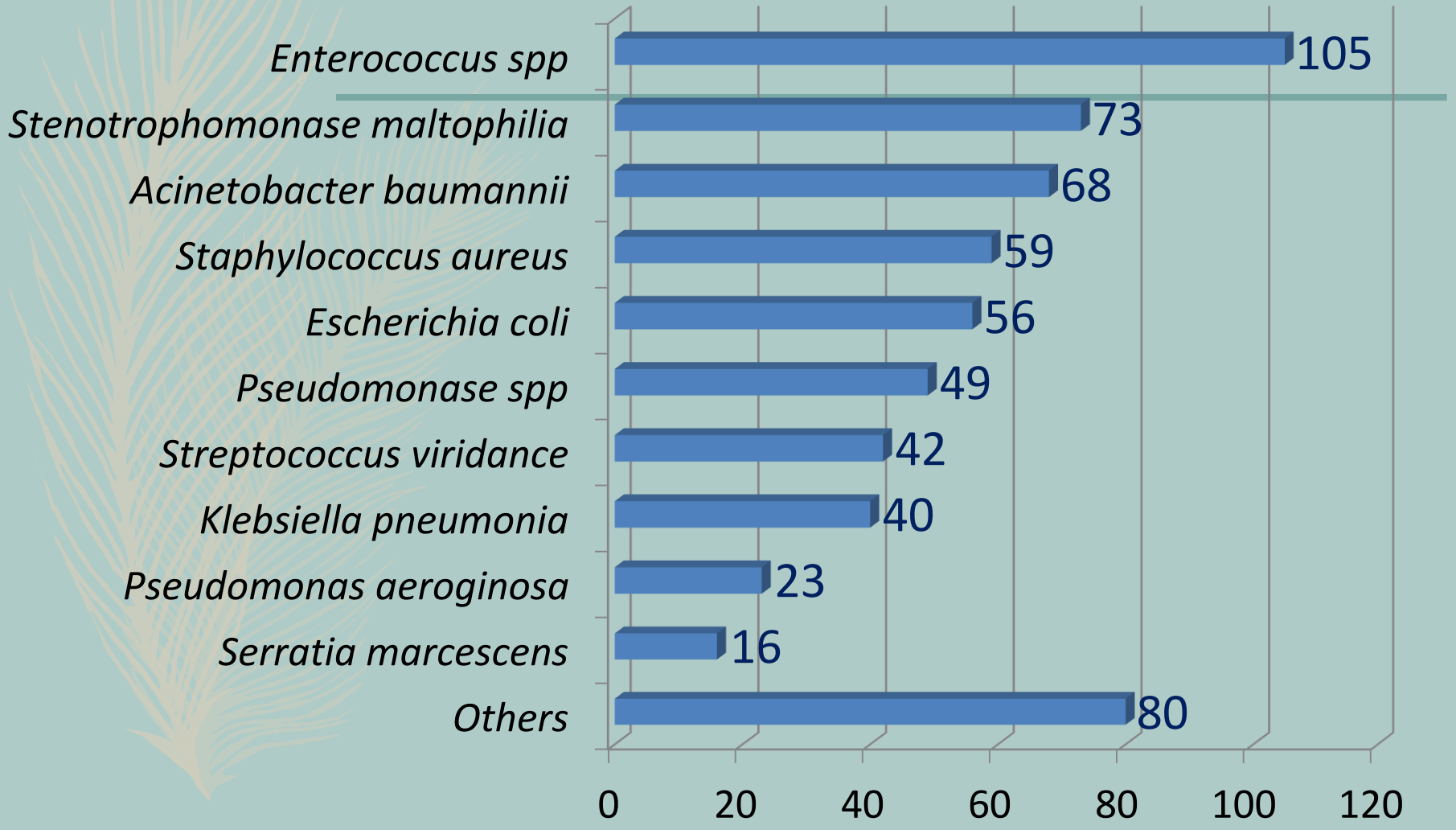
Salmonella spp	5	0.32%	---	---	---	---	5	0.20%
Other g+	670	---	---	---	6	---	676	26.44%
Other g-	18	---	---	---		---	18	0.70%
Other	112	2.34%	---	---	---	---	112	4.38%
Total	1485	---	858	---	117	---	2460	100%

The most common pathogenic bacteria , N=355 (2014)



The most common pathogenic bacteria , N=611 (2015)



7 Staphylococcus aureus

- The biggest Killer
- Most important among Gram positive Organisms
  - *hard to manage*
  - *High antibiotic resistance rate*
- The most important problem is Antibiotic Resistances of the organism
- Potency to Invade and Cause metastatic Infections (This can start from only a small focus of infection like a furuncle and be lethal)

8 Staphylococcus aureus

- Clinical?! Classification Of *Staphylococcus aureus*
  - MSSA
  - MRSA (mecA gene)
    - Community-Acquired
    - Health-Care associated
  - VISA
    - outbreaks of VISA and heteroresistant VISA have been reported in France, Spain, and Japan
    - isolated from people (historically, dialysis patients) who had received multiple courses of vancomycin for a MRSA infection
  - VRSA
    - As of May 2014, VRSA had been isolated in 13 adults from 4 states
    - A concern is that most automated antimicrobial susceptibility testing methods commonly used in the United States were unable to detect vancomycin resistance in these isolates

9 Staphylococcus aureus

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~~Penicillin G~~

↓

Cefazolin or Cefalotin

↓

Clindamycin, Ampicillin+sulbactam

↓

..... ± Aminoglycosides

↓

Trimethoprim-sulfamethoxazole

Oxacillin or Nafcillin± .....

..... ± Rifampin

↓

Vancomycin ± .....

↓

Linezolide ± .....

Daptomycin ± .....

Quinupristin-dalfopristin ± .....

10 Staphylococcus aureus

- Clinical?! Classification Of *Staphylococcus aureus*
  - MRSA (mecA gene)
    - Community-Acquired
    - Health-Care associated

11 Staphylococcus aureus

- is second only to CoNS as a cause of health care associated bacteremia
- is one of the most common causes of health care-associated pneumonia in children
- is responsible for most health care-associated surgical site infections.

12 Staphylococcus aureus

- Health care-associated MRSA strains are resistant to
  - *beta-lactamase–resistant (BLR) beta-lactam antimicrobial agents and*
  - *cephalosporins (except the fifth-generation cephalosporin, ceftaroline), as well as to*
  - *antimicrobial agents of several other classes (multidrug resistance)*

PARENTERAL ANTIMICROBIAL AGENT(S) FOR TREATMENT OF BACTEREMIA AND OTHER SERIOUS STAPHYLOCOCCUS AUREUS INFECTIONS

SUSCEPTIBILITY	ANTIMICROBIAL AGENTS	COMMENTS
I. INITIAL EMPIRIC THERAPY (ORGANISM OF UNKNOWN SUSCEPTIBILITY)		
Drugs of choice:	Vancomycin (15 mg/kg Q6-H + nafcillin or oxacillin)	For life-threatening infections (i.e., septicemia, endocarditis, CNS infection); linezolid could be substituted if the patient has received several recent courses of vancomycin
	Vancomycin (15 mg/kg Q8H)	For non–life-threatening infection without signs of sepsis (e.g., skin infection, cellulitis, osteomyelitis, pyarthrosis) when rates of MRSA colonization and infection in the community are substantial
	Clindamycin	For non–life-threatening infection without signs of sepsis when rates of MRSA colonization and infection in the community are substantial and prevalence of clindamycin resistance is low
II. METHICILLIN-SUSCEPTIBLE, PENICILLIN-RESISTANT S. AUREUS (MSSA)		
Drugs of choice:	Nafcillin or oxacillin[,†]	Only for patients with a serious penicillin allergy and Alternatives (depending on clindamycin-susceptible strain
Alternatives (depending on susceptibility results):	Cefazolin*	
	Clindamycin	
	Vancomycin	Only for penicillin- and cephalosporin-allergic patients
	Ampicillin + sulbactam	

1. *From Pickering LK, editor:* Red book: 2015 report of the Committee on Infectious Diseases*, ed 30. Elk Grove Village, IL, 2015, American Academy of Pediatrics*

PARENTERAL ANTIMICROBIAL AGENT(S) FOR TREATMENT OF BACTEREMIA AND OTHER SERIOUS STAPHYLOCOCCUS AUREUS INFECTIONS

SUSCEPTIBILITY	ANTIMICROBIAL AGENTS	COMMENTS
III. MRSA (OXACILLIN MIC, 4 µG/ML OR GREATER)		
A. Health Care–Associated (Multidrug-Resistant)		
Drugs of choice:	Vancomycin + gentamicin	
Alternatives: susceptibility testing results available before alternative drugs are used	Trimethoprim-sulfamethoxazole	
	Linezolid[‡]	
	Quinupristin-dalfopristin[‡]	
	Fluoroquinolones	Not recommended for people younger than 18 yr of age or as monotherapy
B. Community (Not Multidrug-Resistant)		
Drugs of choice:	Vancomycin + gentamicin†	For life-threatening infections
	Clindamycin (if strain susceptible by "D test)	For pneumonia, septic arthritis, osteomyelitis, skin or soft tissue infections
	Trimethoprim-sulfamethoxazole	For skin or soft tissue infections
Alternatives:	Vancomycin	
IV. VANCOMYCIN INTERMEDIATELY SUSCEPTIBLE OR VANCOMYCIN-RESISTANT S. AUREUS[†]		
Drugs of choice:	Optimal therapy is not known	Dependent on in vitro susceptibility test results
	Linezolid[‡]	
	Daptomycin[?]	
	Quinupristin-dalfopristin[‡] Tigecycline‡	
Alternatives:	Vancomycin + linezolid ? gentamicin	
	Vancomycin + trimethoprim-sulfamethoxazole[†]	

1. *From Pickering LK, editor:* Red book: 2015 report of the Committee on Infectious Diseases, *ed 30. Elk Grove Village, IL, 2015, American Academy of Pediatrics*

15 2 important fact about treatment

- Vancomycin is not recommended for treatment of ~~serious MSSA infections~~, because
  - *outcomes are inferior compared with cases in which antistaphylococcal beta lactams are used and*
  - *to minimize emergence of vancomycin resistance*
- First- or second-generation cephalosporins (eg, cefazolin) or vancomycin are less effective than nafcillin or oxacillin for treatment of MSSA endocarditis or meningitis.
- STAPHYLOCOCCAL INFECTION ≠ VANCOMYCIN

16 Other Facts

- A patient with MSSA infection (and no evidence of endocarditis or central nervous system [CNS] infection) who has a nonserious allergy to penicillin can be treated with a first- or second-generation cephalosporin or with clindamycin, if the *S aureus* strain is susceptible.
- Intravenous vancomycin is recommended for treatment of serious infections caused by staphylococcal strains resistant to BLR beta-lactam antimicrobial agents (eg, MRSA and all CoNS).
- For empiric therapy of life-threatening *S aureus* infections, initial therapy should include vancomycin and a BLR beta-lactam antimicrobial agent (eg, nafcillin, oxacillin).
- For hospital-acquired CoNS infections, vancomycin is the drug of choice.

Susceptibility Rate (%) of Staphylococcus aureus isolated from blood			
Antibiotics	Pouladfar, et al,, 2013-2014 Shiraz (1)	Pourabbas, et al,, 2010-2011, Iran(2)	Soltani, et al, 2016, Kurdistan(3)
Pencillin G	1.4	4	---
Erythromycin	29.4	58	40
Oxacillin	31.4	65	72
Cefoxitin	34.5	-	--
Clindamycin	37.2	76	42
Cefepime	37.8	-	---
Ciprofloxacin	38.9	66	22
Gentamycin	44.3	68	34
Rifampin	59.4	90	---
TMP-SMX	62.6	58	40
Linezolid	100	98	--
Vancomycin	100	100	100
Cefalotin	-	67	60
Amikacin	-	68	50
quinupristin-dalfopristin	-	100	--

1. **Poorabbas B, Mardaneh J, Rezaei Z, et al. Nosocomial Infections: Multicenter surveillance of antimicrobial resistance profile of Staphylococcus aureus and Gram negative rods isolated from blood and other sterile body fluids in Iran. Iranian journal of microbiology. 2015;7(3):127.**

1. Pouladfar G, Jafarpour Z, Abasie P, et al. Report of Antibiotic-Susceptibility Profile of Bacterial Pathogens Causing Bloodstream Infections in Shiraz, 2013 & 2014. Publication of Professor Alborzi Clinical Microbiology Research Center, Annual Report: Professor Alborzi Clinical Microbiology Research Center, Shiraz University of Medical Center, Shiraz, Iran; 2016. p. 19.

2.Soltani J, Poorabbas B, Aminzadeh, M. Antibiotic Resistance Surveillance of Bacteria Isolated from sterile body sites and its clinical outcomes in Tohid and Besat Sanandaj Tertiary Hospitals in 2016-2017, Unpublished Data

MRSA Prevalence's in Iran

- The Prevalence of MRSA Strains in Clinical Samples (Nosocomial?)
- The pooled prevalence of MRSA infections among confirmed S. aureus isolates is predicted to be 43.0 (95% CI 36.3-50.0)

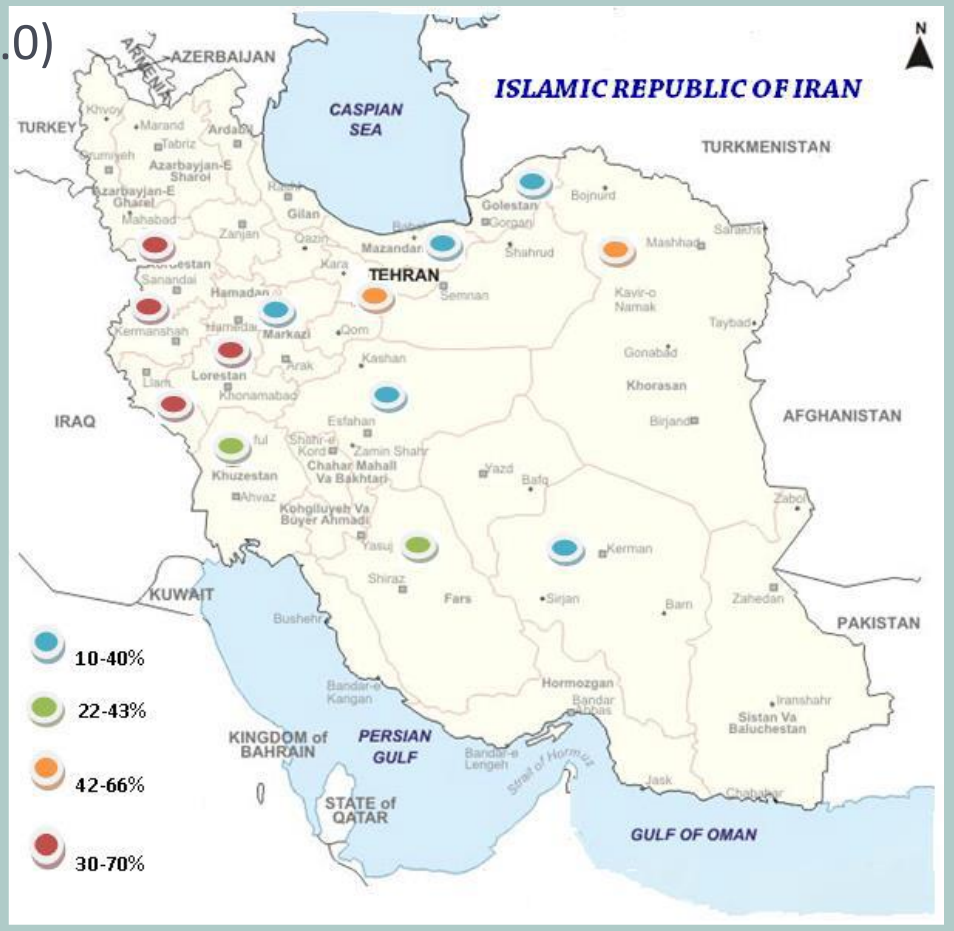


Figure 1: Distribution of MRSA infections in different parts of Iran.
Marked heterogeneities between studies

1. Dadashi M, Nasiri MJ, Fallah F, et al. Methicillin-Resistant Staphylococcus aureus (MRSA) in Iran: A Systematic Review and Meta-analysis. Journal of Global Antimicrobial Resistance.

Staphylococcus aureus: Resistance to methicillin (MRSA) Eastern Mediterranean Region

Countries, territories and other areas or groupings	Data source[b, c, d]	Resistance (%)	No. tested isolates	Type of surveillance, population or samples[c]	Period for data collection	Year of publication or report
Afghanistan	No information obtained for this report					
Bahrain	National data	10	109		2012	2013
Djibouti	No information obtained for this report					
Egypt	National data not available					2013
Egypt	National surveillance (Hospital network)[e]	46	122	Health-care associated infections	2002–2010	2013
Iran (Islamic Republic of)	National data	53	2690	Invasive isolates	2012	2013
Iraq	Publication (*182*)	46.1	657	Clinical samples	2005–2009	2011
Iraq	Publication (*134*)	84	79	Blood isolates (neonate intensive care unit)		2013
Jordan	National data not available					2013
Kuwait	Publication (*183*)	32	1846	13 hospital (hospitalized patients and outpatients)	2005	2008
Lebanon	National data not available					2013
Lebanon	Publication (*32*)	20	479	Clinical isolates	2010–2011	2012
Libya	Publication (*184*)	31	200	Clinical isolates	2007	2011
Morocco	National data	6.2	16	Hospital isolates	2012	2013
Morocco	Publication (*185*)	52.9	31	Intensive care unit	2002–2005	2008
Morocco	Publication (*186*)	19	461	Hospital samples	2006–2008	2009
Oman	National data	50	751	Comprehensive	2012	2013
Pakistan	National data, incomplete	12				2013
Pakistan	Publication (*187*)	28	1102	Clinical isolates	2006–2008	2011
Pakistan	Publication (*188*)	72.2	346	Clinical isolates	2004–2006	2008
Pakistan	Publication (*39*)	38.4	52	Intensive care unit	2007	2010
Pakistan	Publication (*47*)	30.7	289	Vaginal swabs	2004–2006	2008
Pakistan	Publication (*189*)	1.5	85	MRSA carriage among health-care workers	2007–2008	2010
Pakistan	Publication (*187*)	38.1	1102	Hospital isolates	2006–2008	2011
Pakistan	Publication (*190*)	52.6	38	MRSA carriage among hospital patients	2007	2009
Qatar	Publication (*49*)	13.2	53	Blood isolates	2007–2008	2012
Qatar	Publication (*191*)	0.2	514	Student carriers		2010
Saudi Arabia	Publication (*192*)	92	112	Health-care staff	2007	2010
Saudi Arabia	Publication (*148*)	22.3	166	Hospital isolates	2004–2007	2009
Saudi Arabia	Publication (*193*)	39.5	186	Hospital patients	2009–2010	2012

Ref.: World Health Organization. Antimicrobial resistance: global report on surveillance: World Health Organization; **2014**.

MRSA Prevalence Globally

20

Data sources based on at least 30 tested isolates[a]	Overall reported range of resistant proportion (%)	Reported range of resistant proportion (%) in invasive isolates[b] (no. of reports)
African Region		
– National data (n=9 countries)	12–80	52 (n=1)
– Publications (n=27) from 10 additional countries	0–100	33–95 (n=3)
Region of the Americas		
– National data or report to ReLAVRA (n=15 countries)	21–90	
– National networks (n=2) no additional country	21–84	
– Publications (n=17) from 7 additional countries	2.4–90	43–45 (n=2)
Eastern Mediterranean Region		
– National data (n=4 countries)	10–53	53 (n=1)
– Hospital network[c] (n=1) from 1 additional country	46	
– Publications (n=31) from 10 additional countries	0–92	13–18 (n=3)
European Region		
– National data or report to EARS-Net n=36 countries)	0.3–60	0.3–6 (n=32)
– Publications (n=5) from 2 additional countries	27–80	27–50 (n=3)
South-East Asia Region		
– National reports (n=3 countries)	10–26	
– Publications (n=25) from 4 additional countries	2–81	37 (n=1)
Western Pacific Region		
– National data (n=16 countries)	4–84	
– Institute surveillance (n=2 from one additional country)	1–4	
– Publications (n=1) from one additional country	60	

Ref.: World Health Organization. Antimicrobial resistance: global report on surveillance: World Health Organization; **2014**.

VRSA, VISA Definition

– Recommendations for Detecting of *Staphylococcus aureus* With Decreased Susceptibility to Vancomycin

Definitions:

- **Vancomycin-susceptible *S aureus***
  - *MIC 2 µg/mL or less*
- **Vancomycin-intermediately susceptible *S aureus* (VISA)**
  - *MIC 4 through 8 µg/mL*
  - *Not transferable to susceptible strains*
- **Vancomycin-resistant *S aureus* (VRSA)**
  - *MIC 16 µg/mL or greater*
  - *Potentially transferable to susceptible strains*
- **Confirmation of VISA and VRSA**
  - *Possible VISA and VRSA isolates should be retested using vancomycin screen plates or a validated MIC method.*

From Pickering LK, editor: Red book: 2015 report of the Committee on Infectious Diseases, *ed 30. Elk Grove Village, IL, 2015, American Academy of Pediatrics*

22 VRSA or VISA prevalence

- Vancomycin resistance (VRSA), defined as MIC VA>8µg/ml, and vancomycin-intermediate resistance (VISA)
  - Dr. Pourabbas et al. (2015):
    - *Of the 224 S. aureus isolates: no VRSA or VISA*
  - Dr. **Koupah** et al. (2016):
    - *Of the 220 S. aureus isolates: no VRSA or VISA*

1. Poorabbas B, Mardaneh J, Rezaei Z, et al. Nosocomial Infections: Multicenter surveillance of antimicrobial resistance profile of Staphylococcus aureus and Gram negative rods isolated from blood and other sterile body fluids in Iran. Iranian journal of microbiology. **2015**;7(3):127.
2. Koupahi H, Jahromy SH, Rahbar M, Eslami P, Khodadadi E. A study on prevalence of Methicillin and Vancomycin resistance among Staphylococcus aureaus isolates in an Iranian 1000-bed tertiary Care Hospital. Health Sciences. **2016**;5(3):105-9.

23 VRSA or VISA prevalence

- Vancomycin resistance (VRSA), and vancomycin-intermediate resistance (VISA)
  - A systematic Review by Dr. Askari and co-worker (2012)[1]
    - *Out of the 3484 records found in mentioned resources, 13 related studies were included in the final analysis. The result showed that at least 24 VRSA isolates which have been reported from Iran up to September 2012.*

1. Askari E, Zarifian A, Pourmand M, Naderi-Nasab M. High-level vancomycin-resistant Staphylococcus aureus (VRSA) in Iran: A systematic review. Journal of Medical Bacteriology. **2015**;1(3-4):53-61.

24 VRSA or VISA prevalence

- The CDC has recently confirmed the 13th case of VRSA infection since 2002 in the United States.
- VRSA infection continues to be a rare occurrence.
- A few existing factors seem to predispose case patients to VRSA infection, including:
  - *Prior MRSA and enterococcal infections or colonization*
  - *Underlying conditions (such as chronic skin ulcers and diabetes)*
  - *Previous treatment with vancomycin*

https://www.cdc.gov/HAI/settings/lab/vrsa_lab_search_containment.html

Gram-Negative Bacteria-ESBL

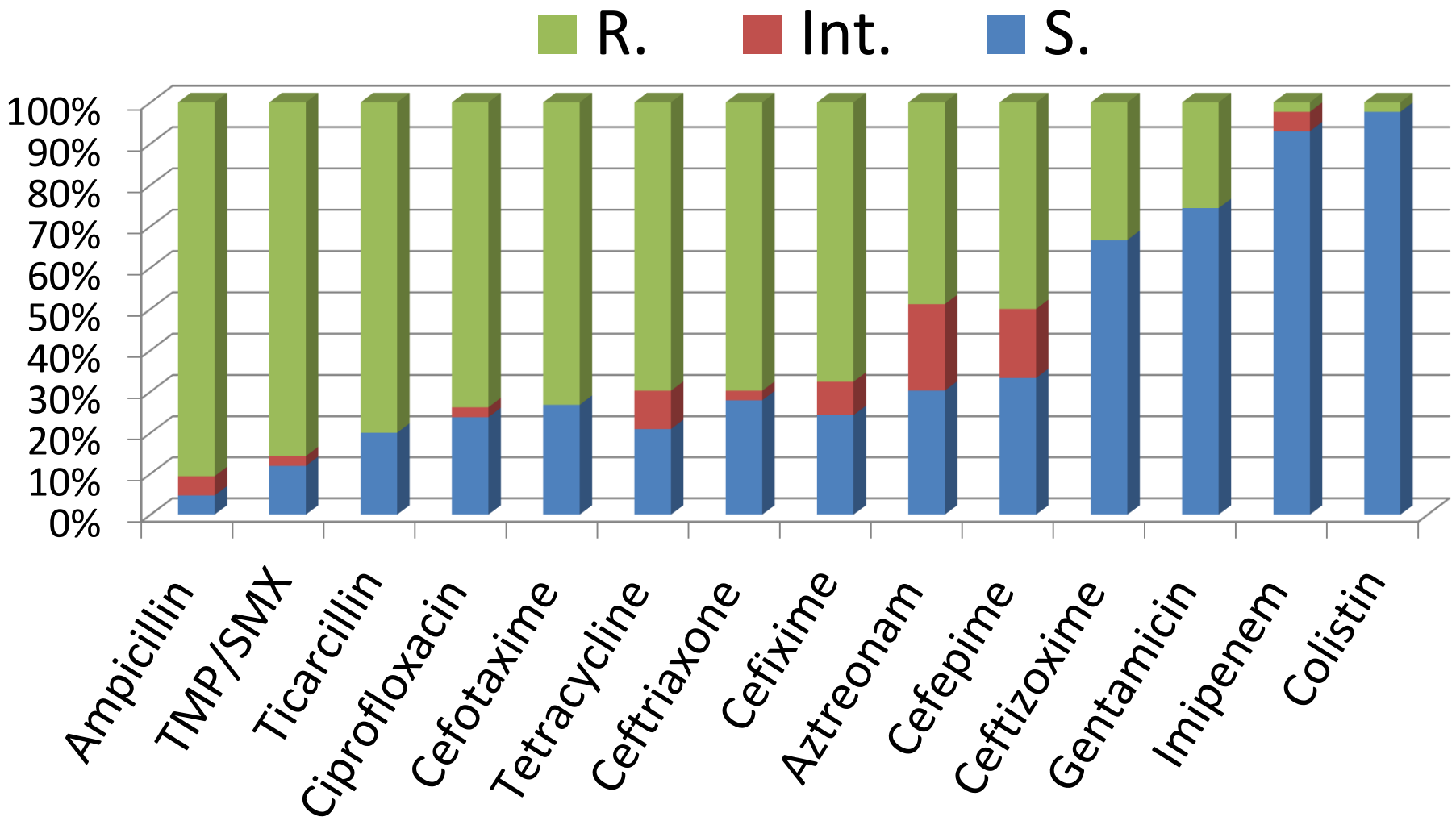
The frequency of ESBLs-producing bacteria isolated from blood in Bactec system			
Bacteria	Pouladfar, 2013-2014 Shiraz (1)	Pourabbas, 2010-2011, Iran(2)	Soltani et al, 2015
Entrobacter spp	40 (36.4%)	-	-
Escherichia coli	64.5 (70%)	90 (35%)	5 (33.3)
K. pneumoniae	--	51 (61%)	10 (66.7)

1. Pouladfar G, Jafarpour Z, Abasie P, Amin-Shahidi M, Anvarinejad M, Dehyadegari MA, et al. Report of Antibiotic-Susceptibility Profile of Bacterial Pathogens Causing Bloodstream Infections in Shiraz, 2013 & 2014. Professor Alborzi Clinical Microbiology Research Center, Shiraz University of Medical Center, Shiraz, Iran; 2016.
2. Poorabbas B, Mardaneh J, Rezaei Z, Kalani M, Pouladfar G, Alami MH, et al. Nosocomial Infections: Multicenter surveillance of antimicrobial resistance profile of Staphylococcus aureus and Gram negative rods isolated from blood and other sterile body fluids in Iran. Iranian journal of microbiology. 2015;7(3):127.
3. Soltani J, Poorabbas B, Miri N, Mardaneh J. Health care associated infections, antibiotic resistance and clinical outcome: A surveillance study from Sanandaj, Iran. World journal of clinical cases. 2016;4(3):63.

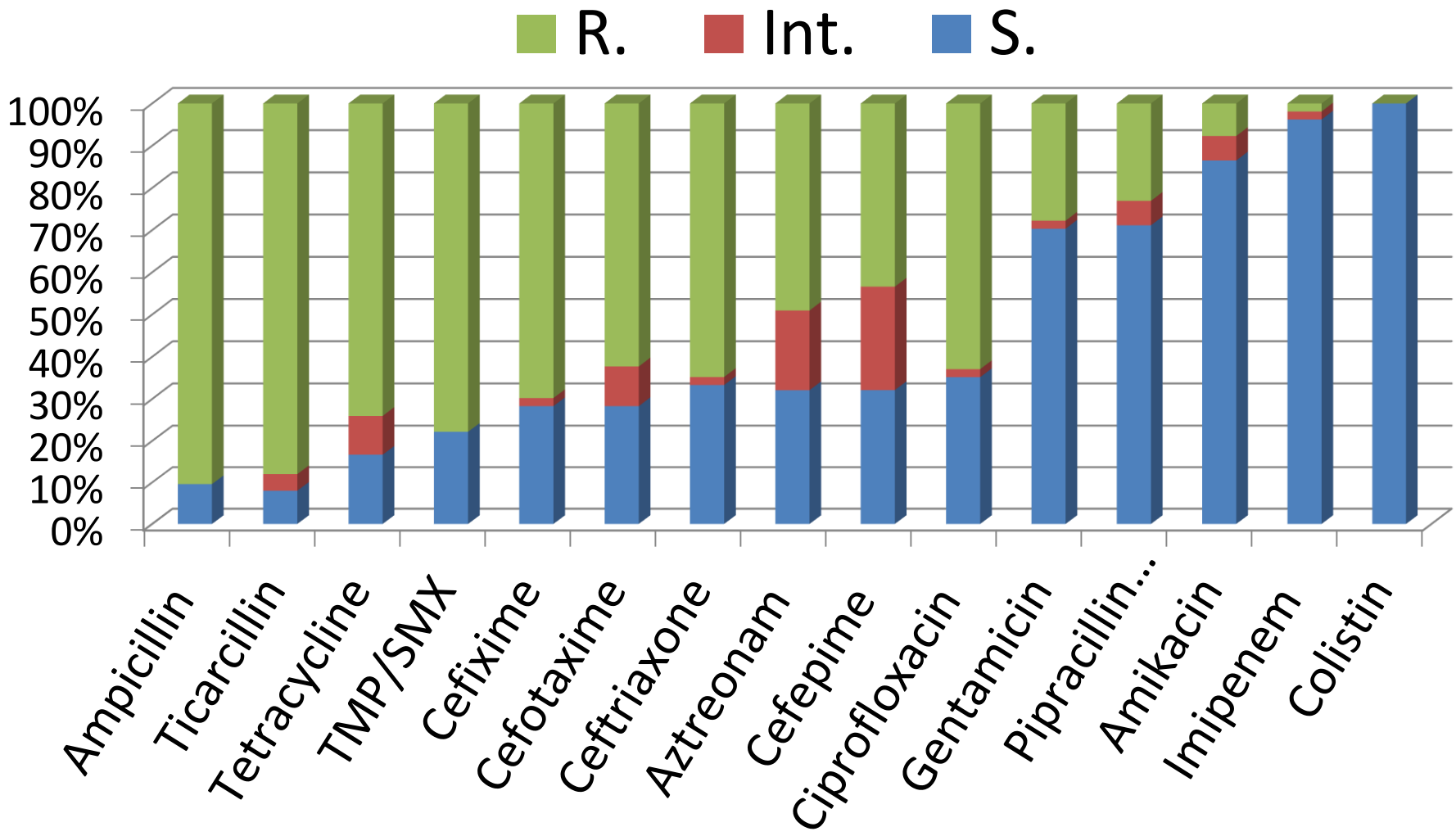
26 Gram-Negative Bacteria-ESBL

- Extended-spectrum β-lactamases (ESBLs) are
  - enzymes that mediate resistance to extended spectrum (third generation) cephalosporins (e.g., ceftazidime, cefotaxime, and ceftriaxone) and monobactams (e.g., aztreonam) but
  - do not affect cephamycins (e.g., cefoxitin and cefotetan) or carbapenems (e.g., meropenem or imipenem).
  - The presence of an ESBLproducing organism in a clinical infection can result in treatment failure if one of the above classes of drugs is used.

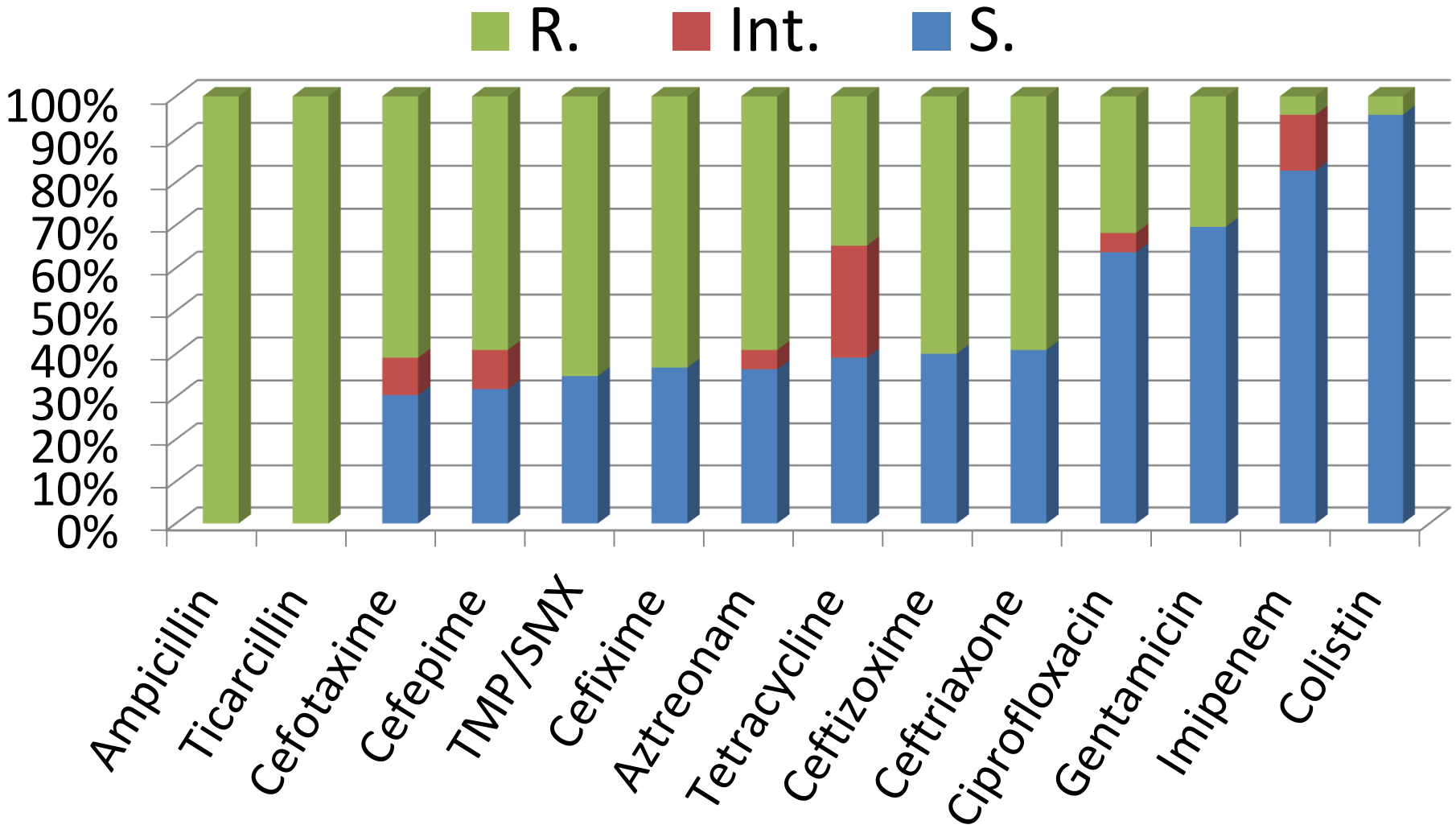
43 *Escherchia coli* (2014)



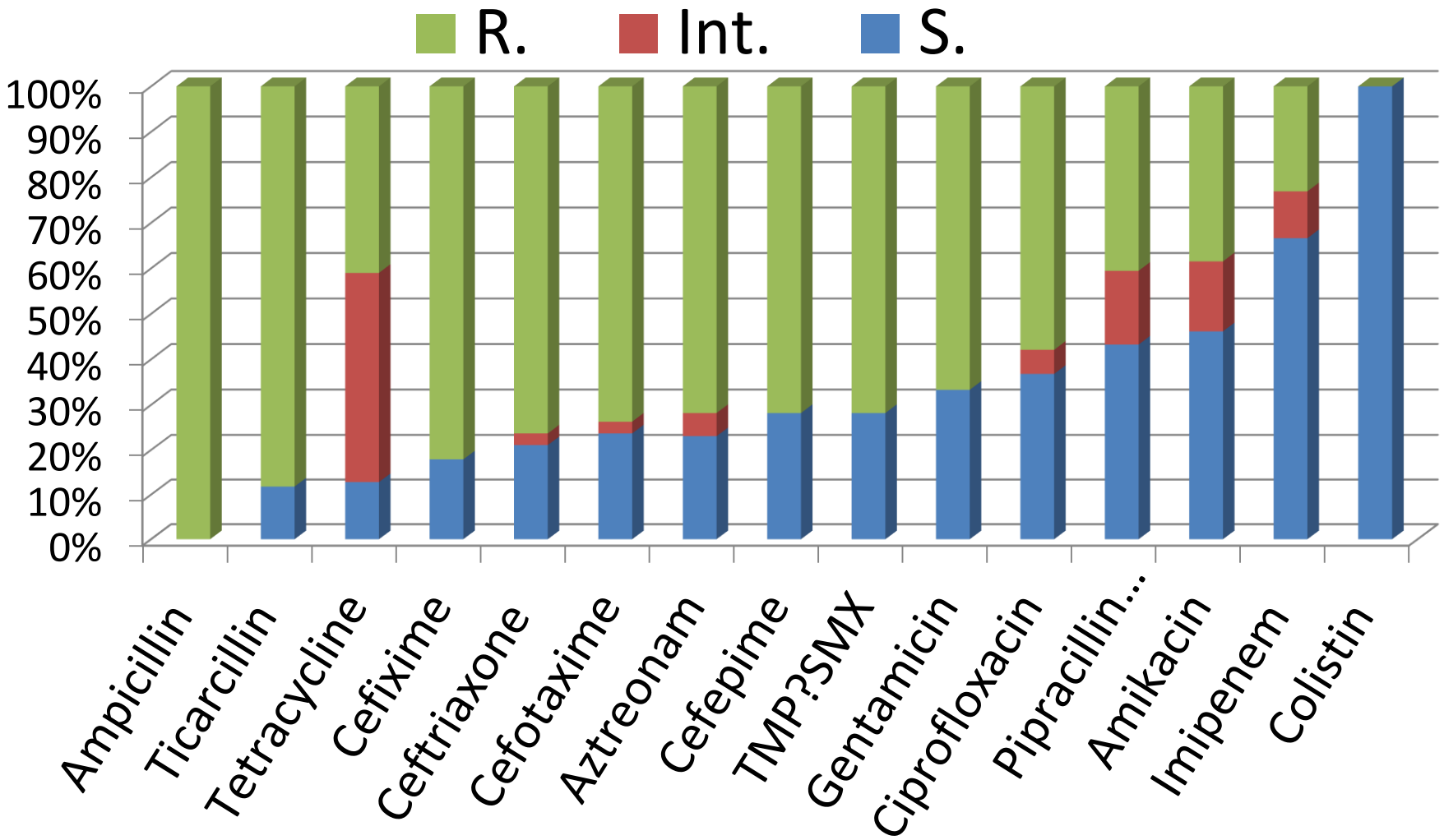
56 *Escherchia* coli (2015)



23 *Klebsiella pneumonia* (2014)



40 *Klebsiella pneumonia* (2015)



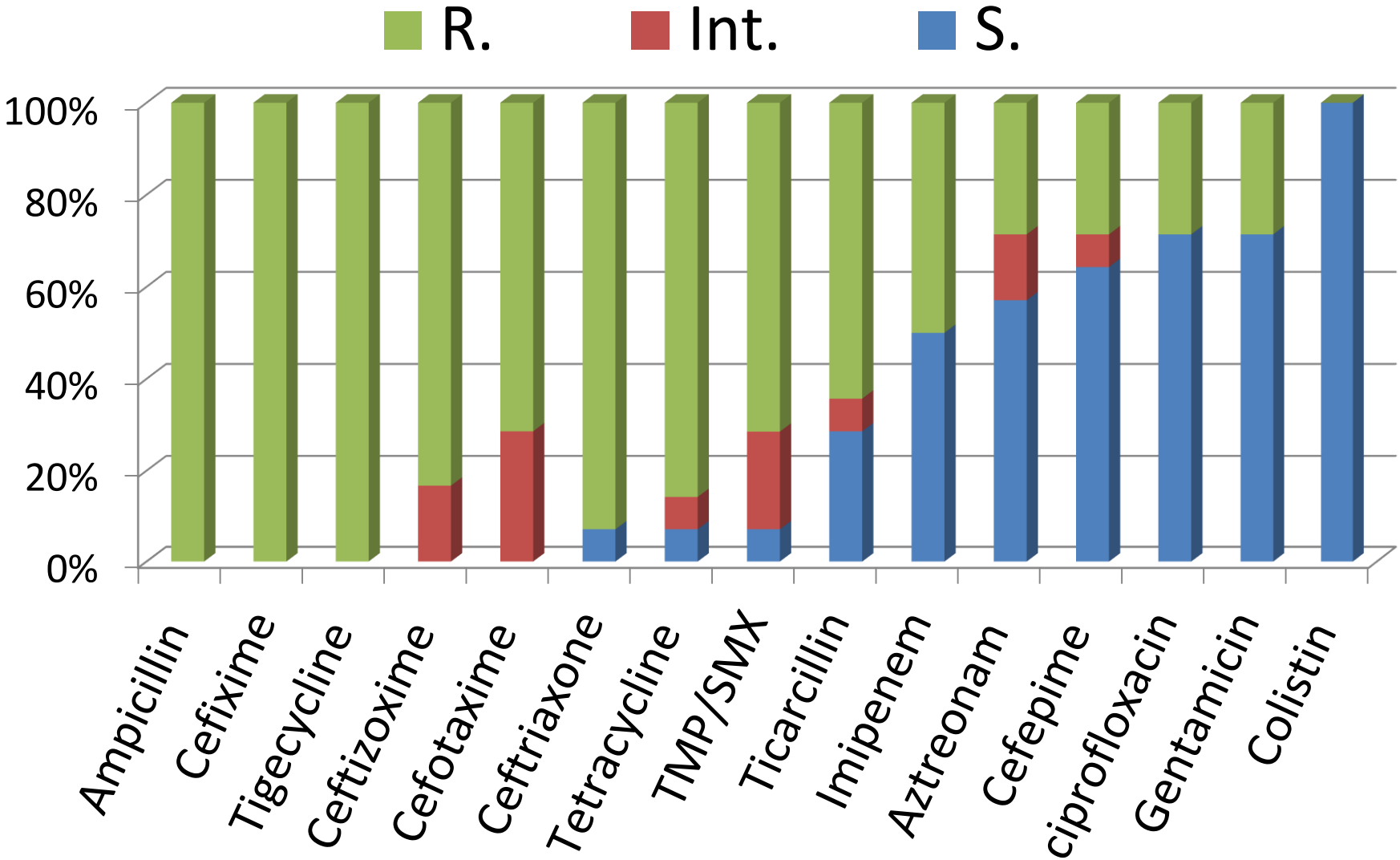
Clinical Implication

- *E. coli* is the most common causes of neonatal sepsis.
- *K. pneumonia* is a common cause of neonatal septicemia with high mortality rate.
- The susceptibility of these organisms to ampicillin and amoxicillin were poor ranging from 6.7% to 20%.
- The current WHO recommendation for empirical prophylaxis and treatment of suspected neonatal sepsis is a combination of ampicillin and gentamicin

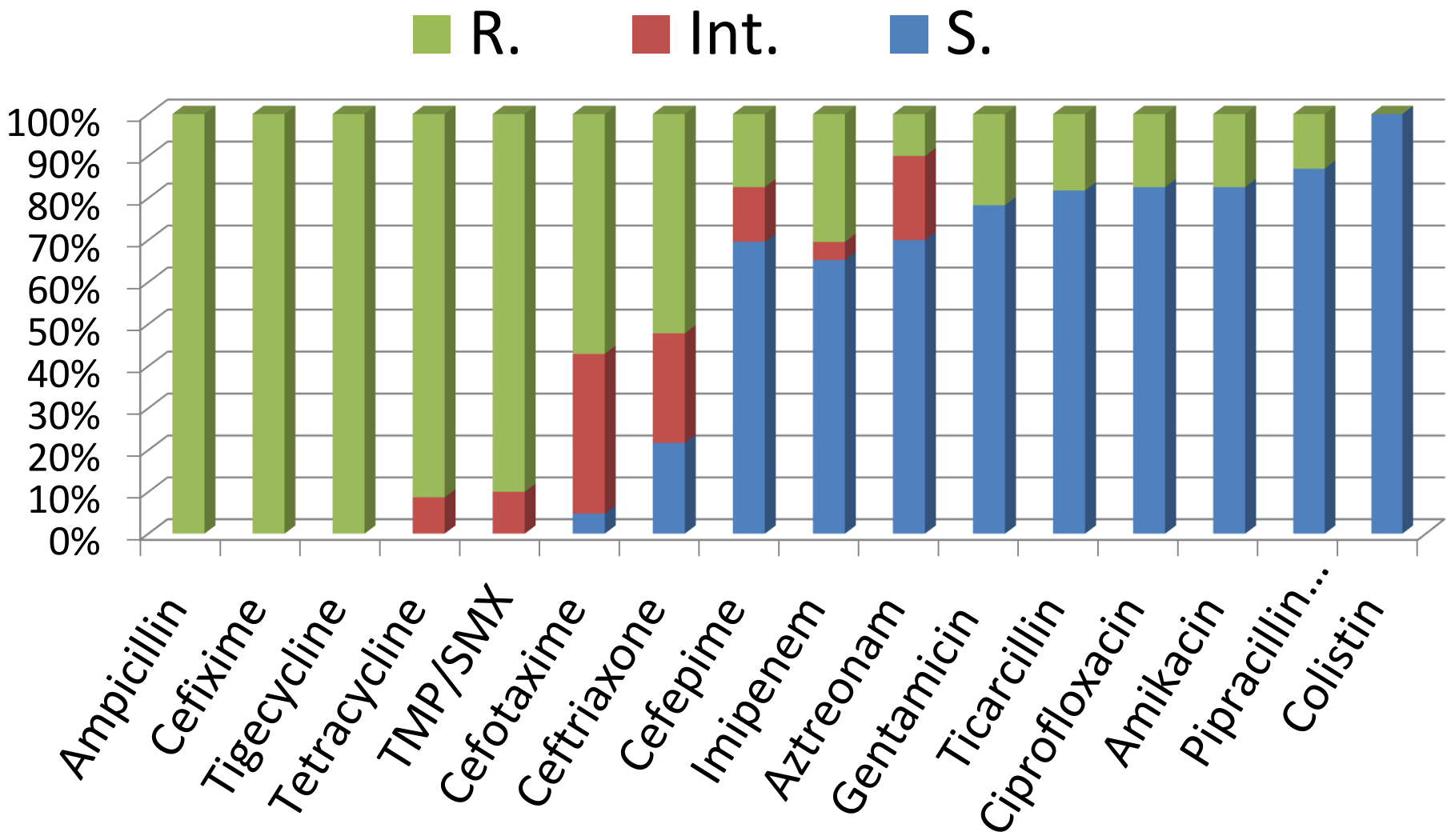
Clinical Implication

- The quality of evidence for the recommendation of sepsis prophylaxis is categorized as weak and very low quality evidence; and for sepsis treatment is categorized as strong and low quality of evidence.
- Nevertheless, the efficacy of this antibiotics combination should be re-assessed considering the higher resistance rates to ampicillin and gentamicin in Iran.

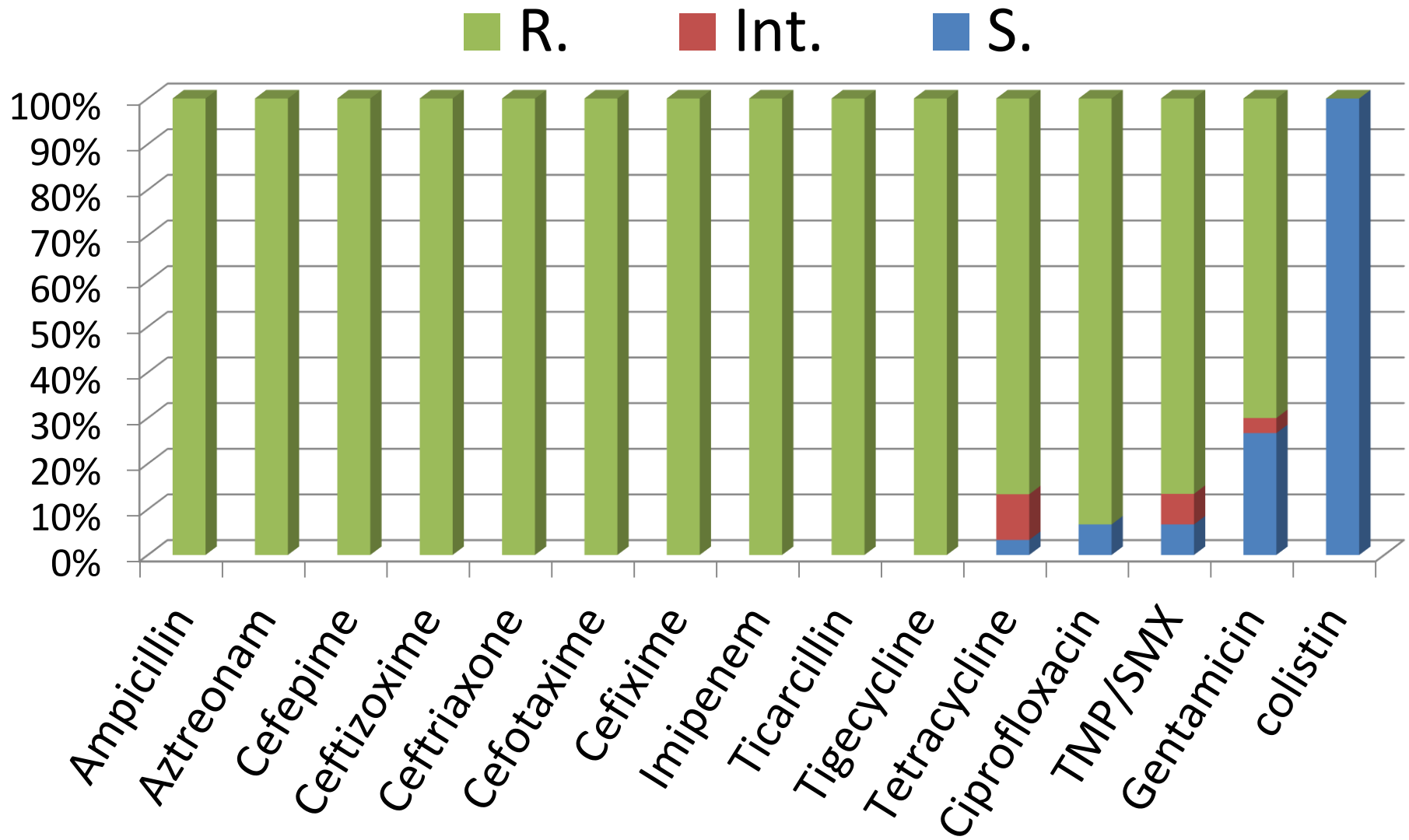
14 Pseudomonas aeroginosa (2014)



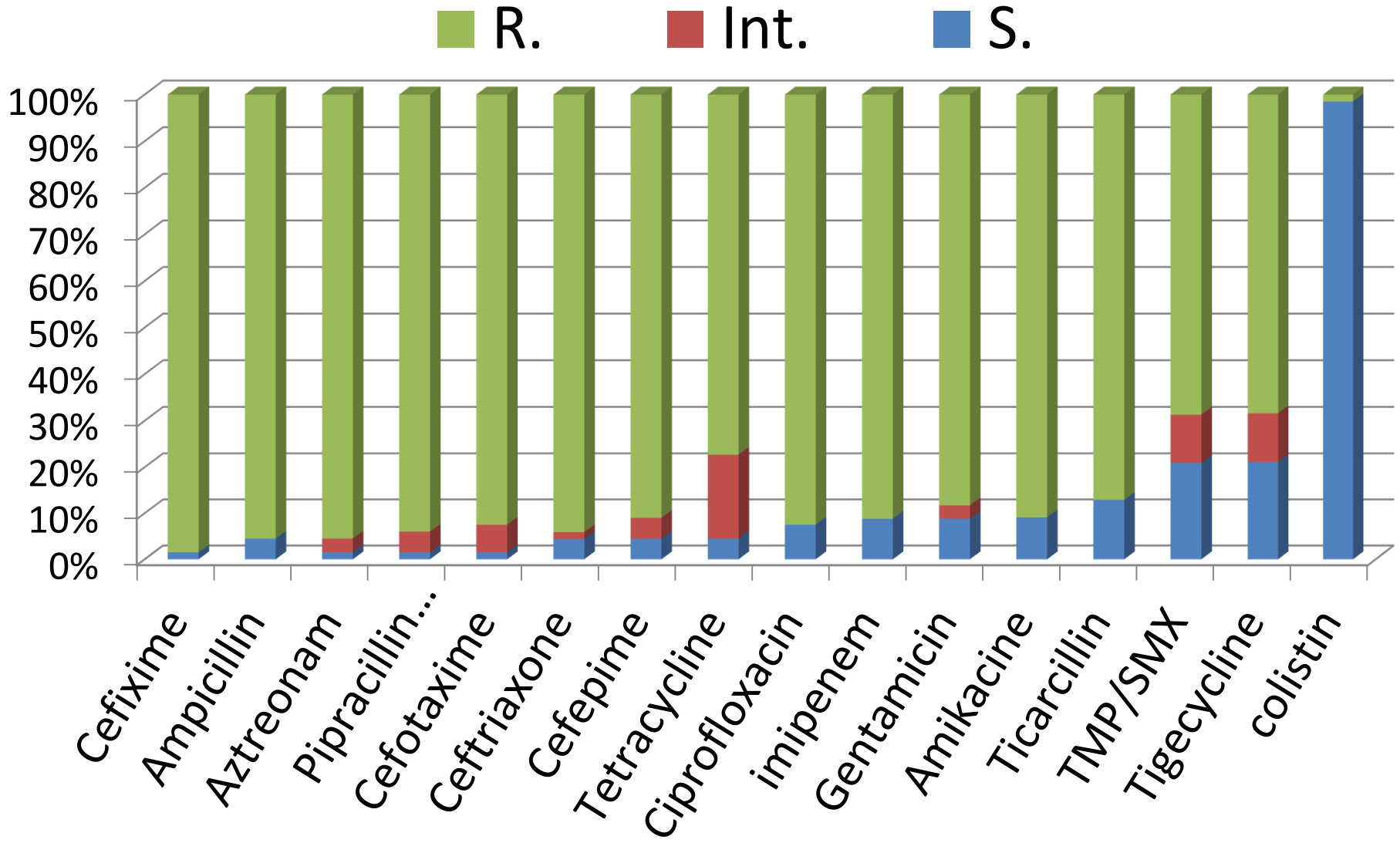
23 Pseudomonas aeroginosa 2015



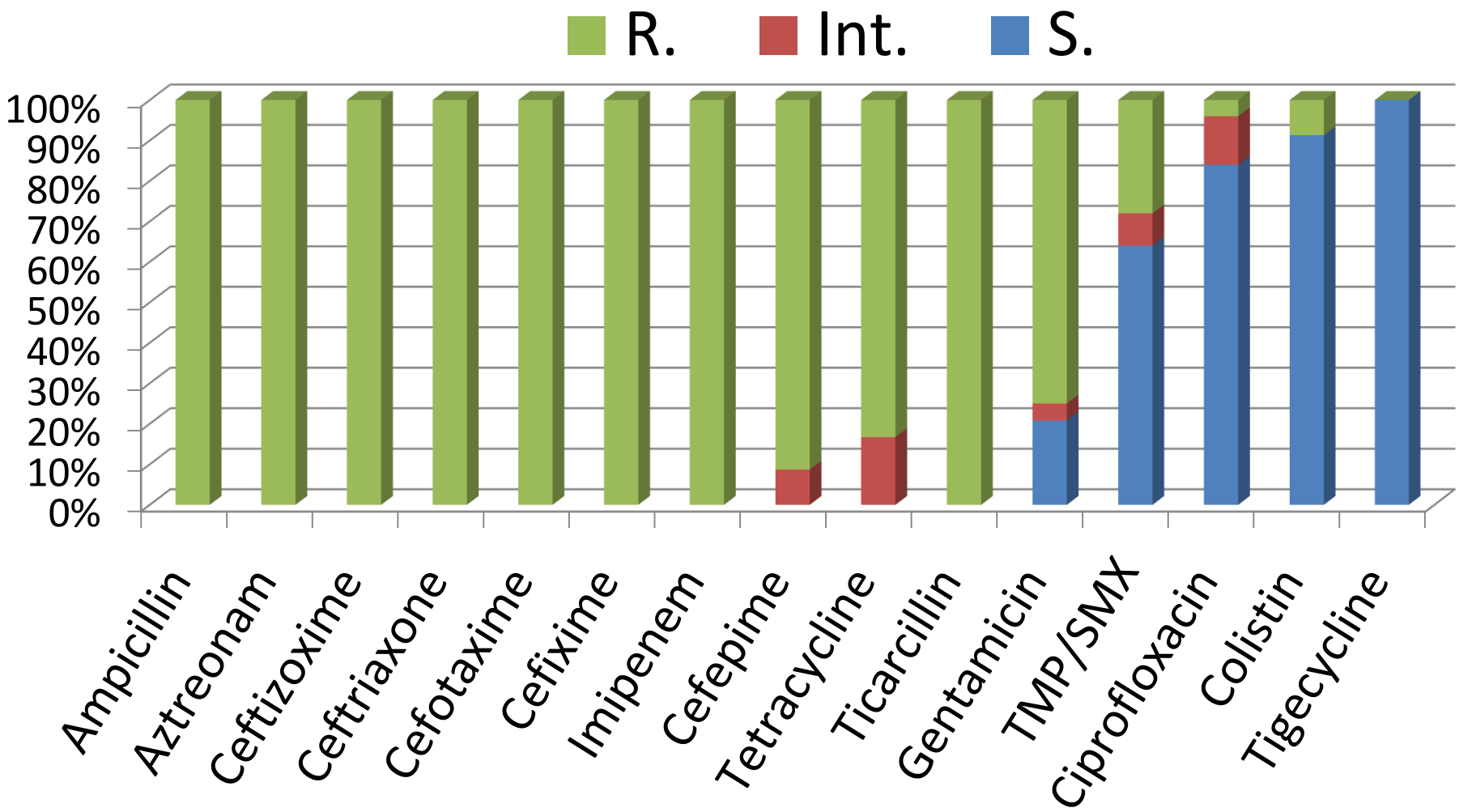
30 *Acinetobacter baumani* (2014)



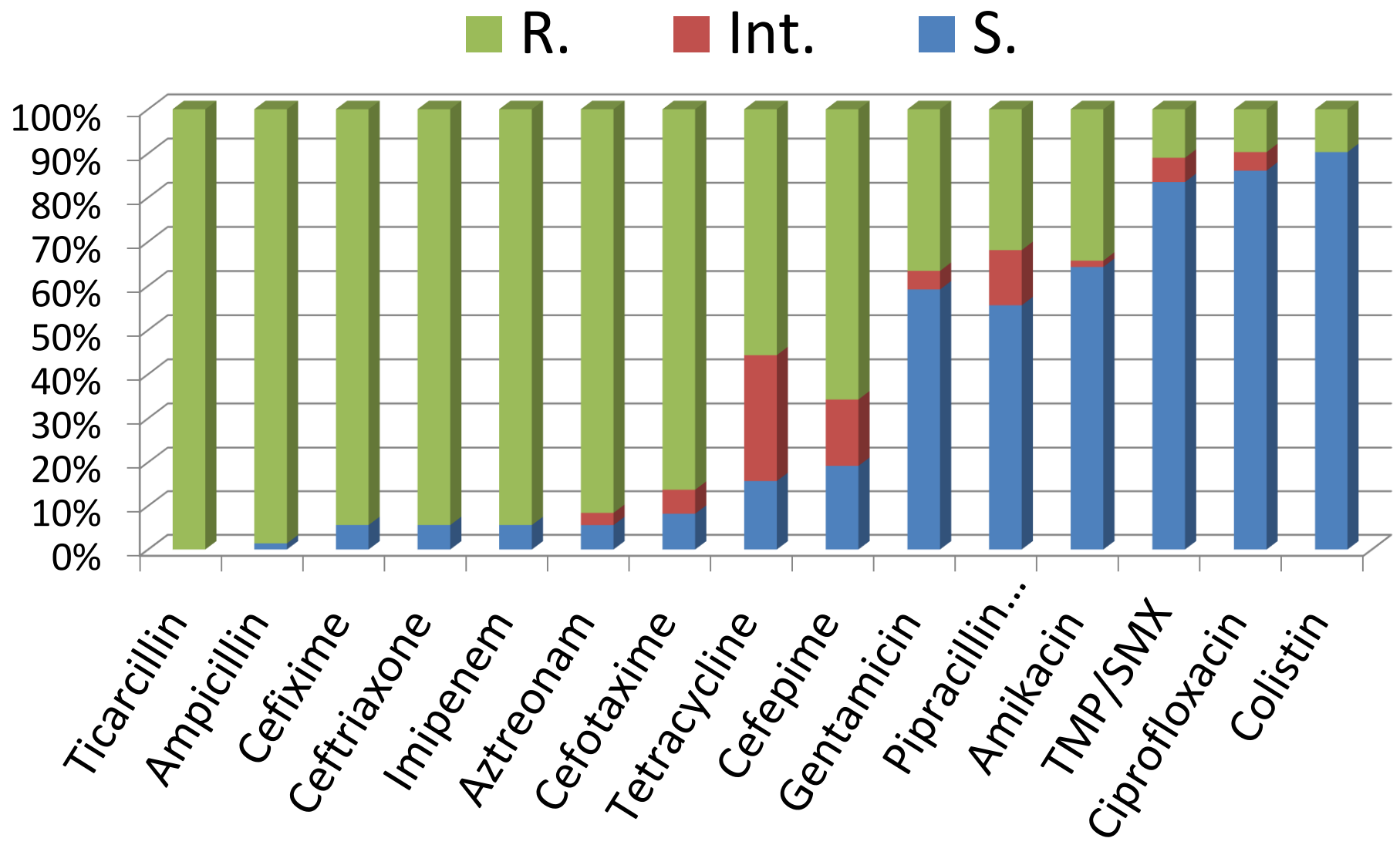
68 *Acinetobacter baumani* (2015)



25 *Stenotrophomonas maltophilia* (2014)



73 *Stenotrophomonas maltophilia* (2015)



39 Conclusion

- Serious bacterial infections that are resistant to commonly available antibiotics have become
  - *A major worldwide healthcare problem*
  - *They are more severe*
  - *Require significantly more expensive diagnosis*
  - *Require longer and more sophisticated treatments*

Conclusion

- According to World Health Organization, Post-Antibiotic Era, in which even mild infections causing serious problems is approaching soon till 2050.

Join Us to Combat Against Antibiotic Resistances and Become an Antibiotic Guardian

Point Prevalence Surveys (PPS) provide useful data on the patterns of in-hospital antimicrobial prescribing and is crucial for changing prescribing practices for antibiotic stewardship programs.

Let Start with Global-PPS Program!?

http://app.globalpps.uantwerpen.be/globalpps_webpps/

AIMS Global-PPS

- Expand the standardized antimicrobial web based PPS at a global scale to collect consistent, valid and comparable antimicrobial prescribing data.
- Monitor rates of antimicrobial prescribing in hospitalized adults, children and neonates.
- Determine the variation in drug, dose and indications of antimicrobial prescribing across continents.
- Identify targets to improve quality of antimicrobial prescribing.
- Help designing hospital interventions to promote prudent antimicrobial use.
- Assess effectiveness of interventions through repeated PPS.
- Increase public health capacity.

Importent research questions

- What is the quantity and quality of antimicrobial prescribing?
  - Geographical distribution and ranges
  - Broad versus narrow spectrum antibiotic use
  - Adults – children - neonates
  - Dose
  - ……
- What are determinants of inappropriate antimicrobial prescribing ?
  - Patient related : age, diagnosis, indication
  - Institutional : hospital type, ward type, national/local policy, existing guidelines, ….
  - Geographical factors: region, country, cultural, availability of drugs on market, prescriber related (training), custum, ….

Any hospital can participate
Ready to join us ?

Contact
Ann Versporten
at global-PPS@uantwerpen.be

URL
~~http~~://app.globalpps.uantwerpen.be/globalpps_webpps/


Any Comment,
Please?!
Thank you for
your Attention


If you want to go Fast, go alone.
If you want to go Far, go together.