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SURVIVING SEPSIS AND RAISING ANTIMICROBIAL RESISTANCE

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DEFINITION OF SEPSIS

- ‘A life threatening organ dysfunction caused by a dysregulated host response to infection’

- World Health Organization 2020

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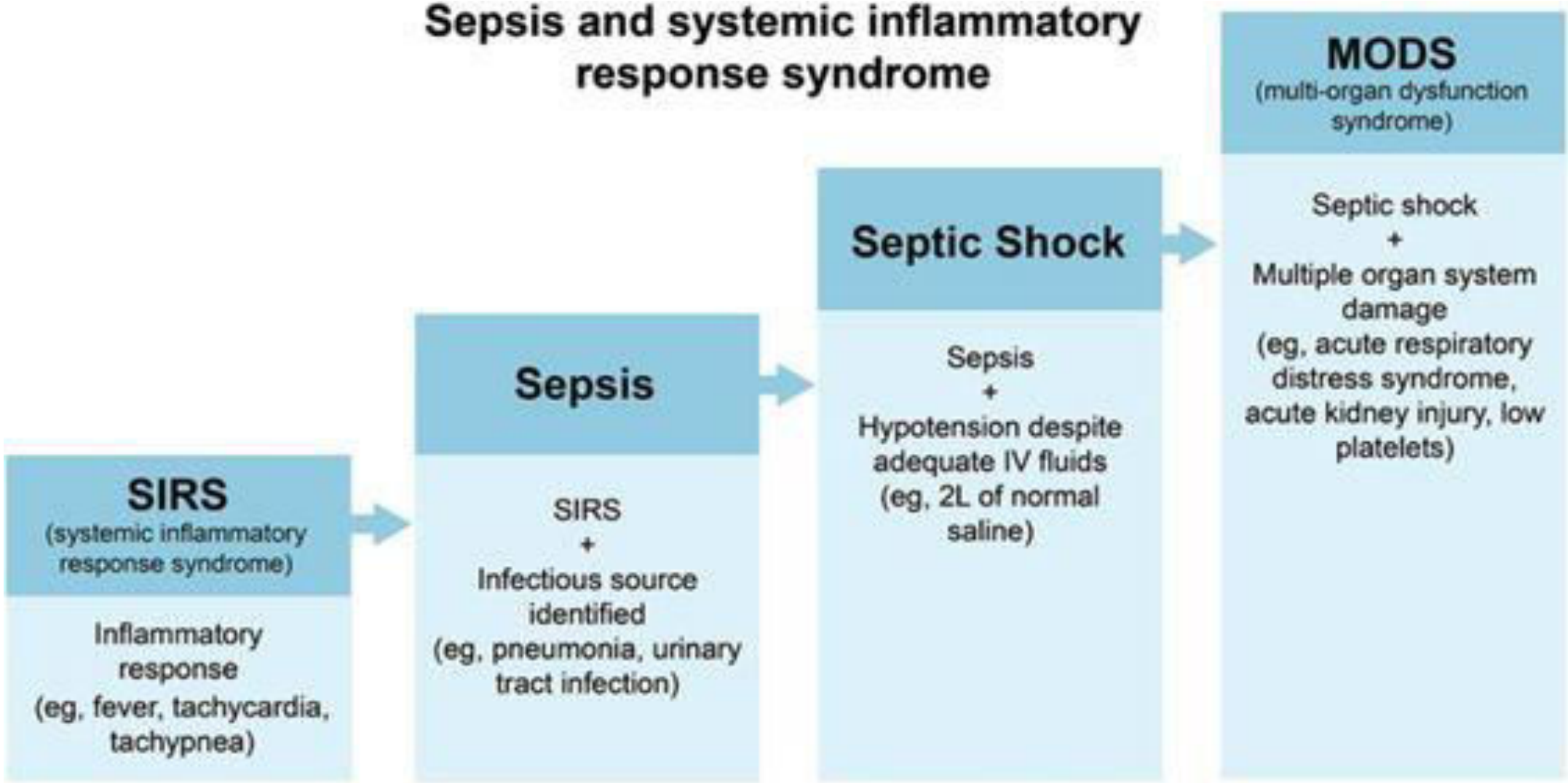
SIRS - SEPSIS - SEPTIC SHOCK - MODS



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SEPSIS AND SEPSIS RELATED DEATHS - AN OVERVIEW

- 48.9 million cases reported world wide
- 11 million sepsis related deaths worldwide
- 20% of global deaths

- 50% of global sepsis cases occurred in children (approx. 20 million cases)
- 2.9 million global deaths occurred in children under five years of age

- 85% sepsis cases and sepsis related deaths occurred in low and middle income countries

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Surviving Sepsis Campaign

Surviving Sepsis Campaign Timeline

2002

Declaration Barcelona

2002 SSC initated between ESICM, SCCM & ISF

2004 Adult Guidelines

2005 working with IHI to create first set of performance improvement bundles.
2008 SSC independent of industry funding and ISF no longer a partner

2006

2008 Adult Guidelines

2010 Data published on 15,000 patients from SSC database demonstrating 20% RRR for death.
2013 sepsis metrics adopted by New York state, USA.

2010

2012 Adult Guidelines

2014 Data published on 30,000 patients from SSC database demonstrating 25% RRR for death.

2014

2016 Adult Guidelines

2017 Data from New York state published on 100,000 patients with 15.2% RRR for death.
2018 Hour-one bundle released.

2018

2021 Adult Guidelines

2018 Sepsis research priorities published
2020 SSC COVID-19 Guidelines

2022

Society of Critical Care Medicine
The Intensive Care Professionals

ESICM

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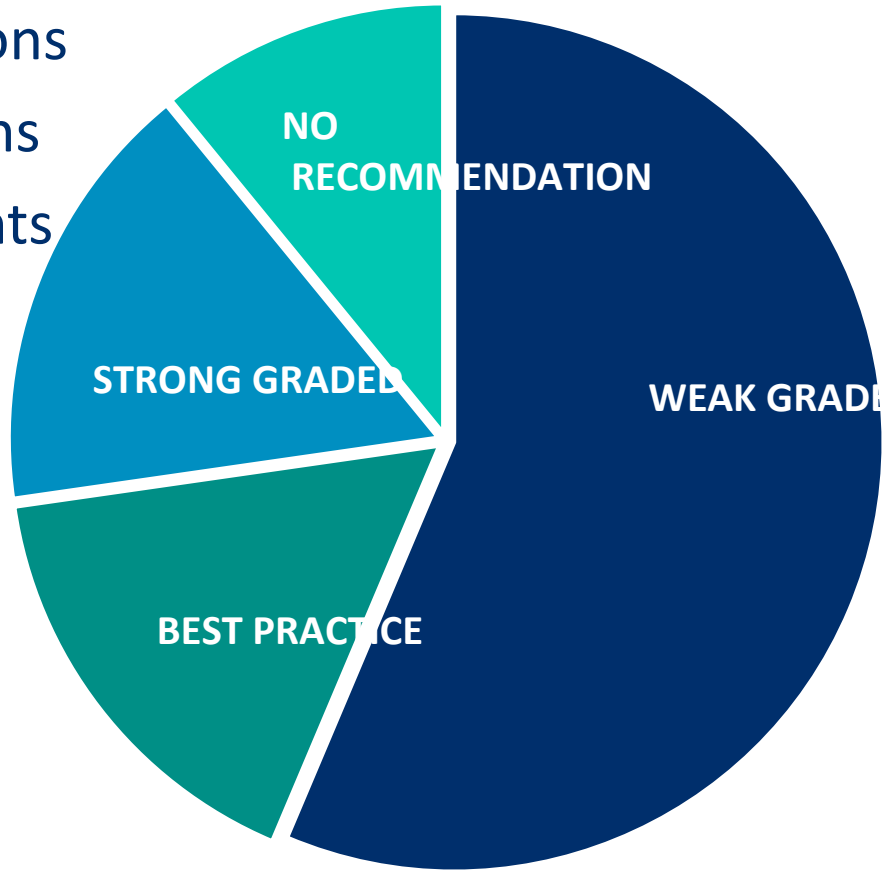
93 RECOMMENDATIONS IN CURRENT SSC

- 32 strong recommendations
- 39 weak recommendations
- 18 best practice statements



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SSC 2021 NEW RECOMMENDATIONS

Several new recommendations regarding –

- Capillary refill time
- Empiric MRSA coverage
- Empiric fungal coverage
- Peripheral vasopressor use
- Levosimendan
- HFNC and NIV
- Use of ECMO
- Post-ICU follow up

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EVOLUTION OF SEPSIS BUNDLES OVER THE YEARS

2005	2013	2018

6-hour Resuscitation Bundle
• Measure serum lactate
• Obtain blood cultures prior to antibiotics
• Administer broad spectrum antibiotics within 3 hours of ED or 1 hour non-ED admission
• With hypotension &/or serum lactate > 4 mmol/L:
  ○ Crystalloid 20ml/Kg
  ○ Vasopressors if unresponsive
• Persistent hypotension &/or lactate > 4 mmol/L achieve:
  • CVP ≥ 8 mm Hg
  • ScvO2 ≥ 70 % or SvO2 ≥ 65%
	3-hour Bundle
	• Measure serum lactate
	• Obtain blood cultures prior to antibiotics
	• Administer broad spectrum antibiotics
	• With hypotension &/or serum lactate > 4 mmol/L:
	  ○ Crystalloid 30ml/Kg
	6-hour Bundle
	• Vasopressors for hypotension after fluid
	• For persistent arterial hypotension after fluid or with lactate > 4 mmol/L;
	  • Measure CVP
	  • Measure ScvO2
		1-hour Bundle
		• Measure serum lactate. Re-measure if initial > 2 mmol/L
		• Obtain blood cultures prior to antibiotics
		• Administer broad spectrum antibiotics
		• Begin rapid crystalloid 30 ml/kg
		• Apply vasopressors if hypotension remains after fluid resuscitation to MAP ≥ 65 mm Hg

24-hour Management Bundle • Low dose steroids • Human activated protein C (rhAPC) • Maintain glucose 70 -150 mg/dL • Maintain median inspiratory plateau pressure < 30 cm H2O in mechanical ventilation	***24-hour Bundle no longer recommended***	

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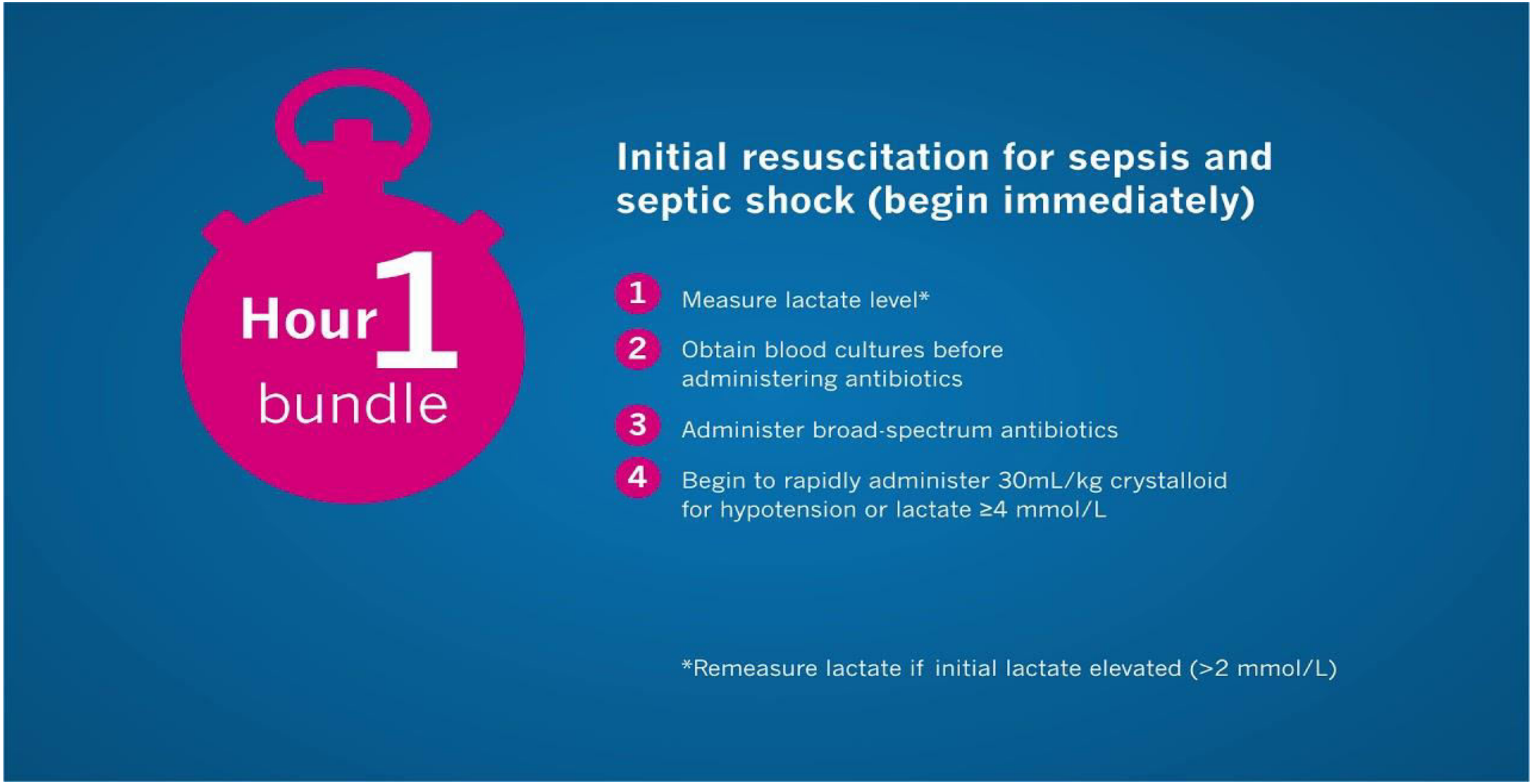
ONE HOUR BUNDLE OF SEPSIS MANAGEMENT



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The Impact of Timing of Antibiotics on Outcomes in Severe Sepsis and Septic Shock: A Systematic Review and Meta-analysis

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Abstract

Objectives—We sought to systematically review and meta-analyze the available data on the association between timing of antibiotic administration and mortality in severe sepsis and septic shock.

Data Sources and Study Selection—A comprehensive search was performed using a pre-defined protocol. Inclusion criteria: adult patients with severe sepsis or septic shock, reported time to antibiotic administration in relation to ED triage and/or shock recognition, and mortality. Exclusion criteria: immunosuppressed populations, review article, editorial, or non-human studies.

Data Extraction—Two reviewers screened abstracts with a third reviewer arbitrating. The effect of time to antibiotic administration on mortality was based on current guideline recommendations: 1) administration within 3 hours of ED triage; 2) administration within 1 hour of severe sepsis/septic shock recognition. Odds Ratios (OR) were calculated using a random effect model. The primary outcome was mortality.

Data Synthesis—1123 publications were identified and 11 were included in the analysis. Among the 11 included studies, 16,178 patients were evaluable for antibiotic administration from ED triage. Patients who received antibiotics more than 3 hours after ED triage (< 3 hours reference), had a pooled OR for mortality of 1.16 (0.92 to 1.46, p = 0.21). A total of 11,017 patients were evaluable for antibiotic administration from severe sepsis/septic shock recognition. Patients who received antibiotics more than 1 hour after severe sepsis/shock recognition (< 1 hour reference) had a pooled OR for mortality of 1.46 (0.89 to 2.40, p = 0.13). There was no increased mortality in the pooled ORs for each hourly delay from <1 to >5 hours in antibiotic administration from severe sepsis/shock recognition.

Conclusion—Using the available pooled data we found no significant mortality benefit of administering antibiotics within 3 hours of ED triage or within 1 hour of shock recognition in severe sepsis and septic shock. These results suggest that currently recommended timing metrics as measures of quality of care are not supported by the available evidence.

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IMPACT OF TIMING OF ANTIBIOTICS – A META ANALYSIS

Odds Ratios For Mortality With Each Hourly Incremental Delay In Antibiotic Administration From Severe Sepsis / Septic Shock Recognition

Author	< 1 hour	1–2 hours	2–3 hours	3–4 hours	4–5 hours	> 5 hours
Ferrer (2014)	Ref	0.94 (0.80, 1.12)	0.89 (0.73, 1.08)	0.92 (0.73, 1.15)	0.97 (0.75, 1.25)	1.38 (1.18, 1.61)
Gaieski (2010)	Ref	1.65 (0.84, 3.20)	1.38 (0.44, 3.96)	1.72 (0.42, 6.36)	4.13 (0.45, 50.6)	0.92 (0.02, 11.82)
Kumar (2006)	Ref	1.67 (1.10, 2.53)	2.59 (1.67, 4.01)	3.01 (1.94, 4.67)	3.98 (2.45, 6.47)	15.23 (11.1, 21.1)
Ryoo (2015)	Ref	0.91 (0.47, 1.75)	1.31 (0.62, 2.71)	1.17 (0.39, 3.14)	1.10 (0.30, 3.39)	1.30 (0.34, 4.13)
Pooled OR (95% CI)	Ref	**1.21 (0.84, 1.72)**	**1.42 (0.76, 2.67)**	**1.53 (0.72, 3.28)**	**1.90 (0.72, 5.01)**	**2.47 (0.46, 13.36)**

Abbreviations: OR – Odds ratio; Ref – reference value; CI – confidence interval.

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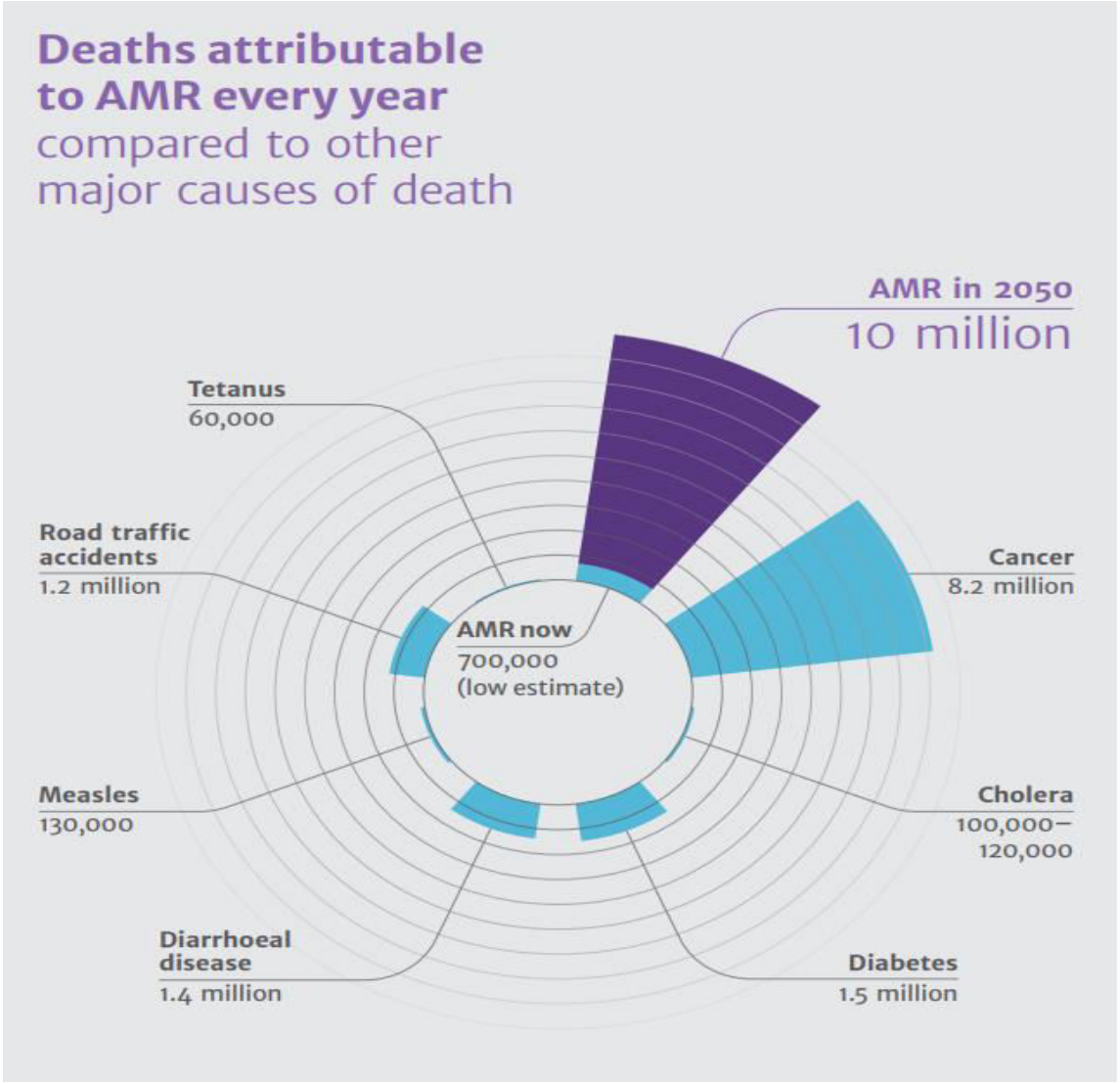
RAISING ANTI MICROBIAL RESISTANCE



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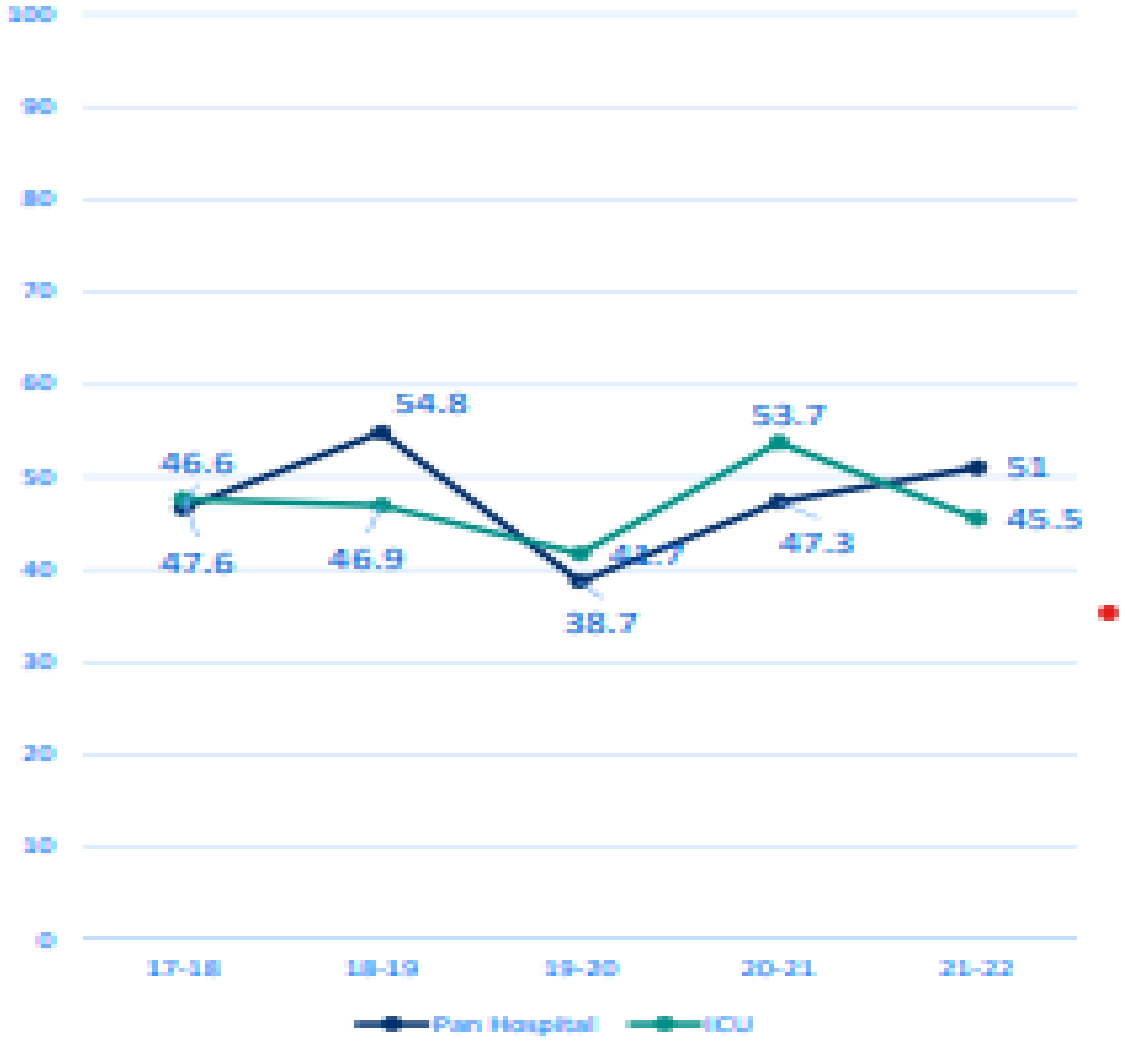
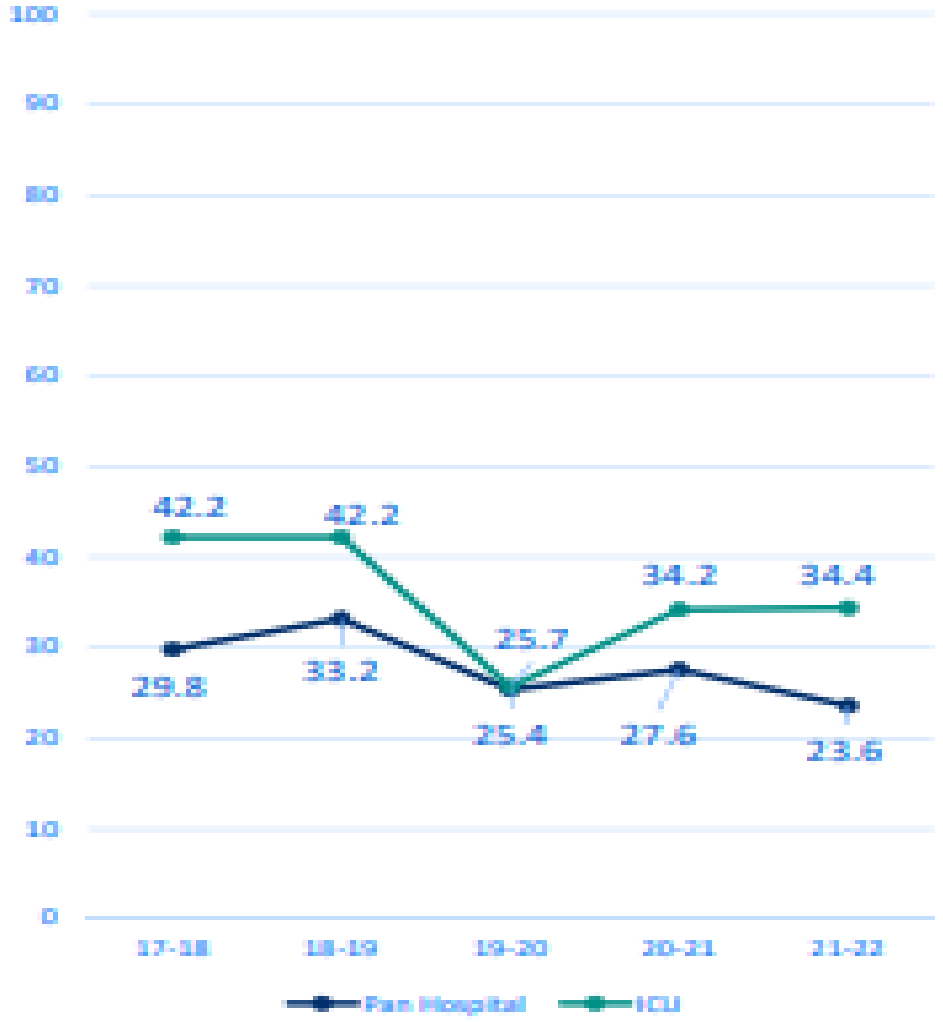
MRSA & VRE

MRSA



VRE



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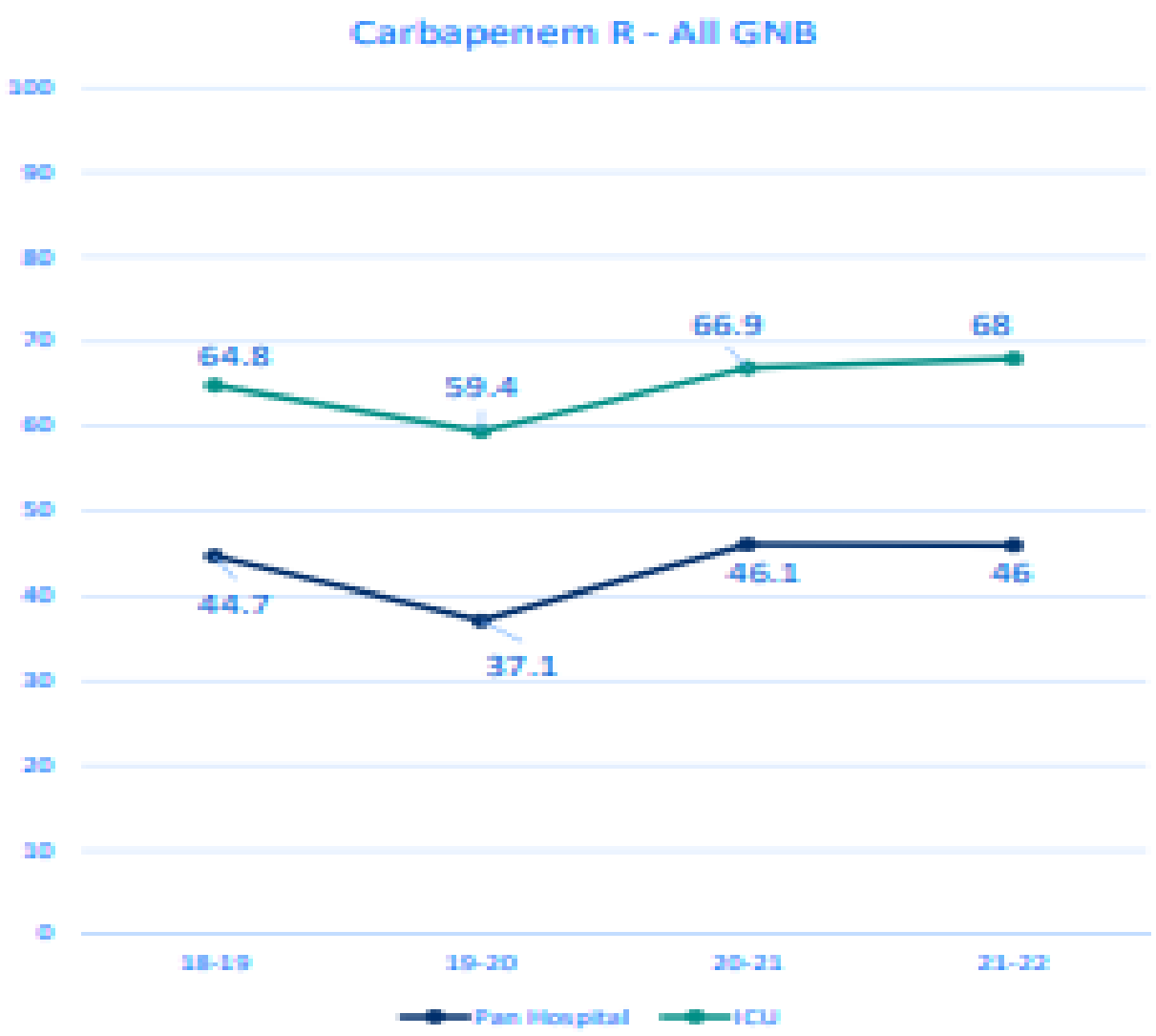
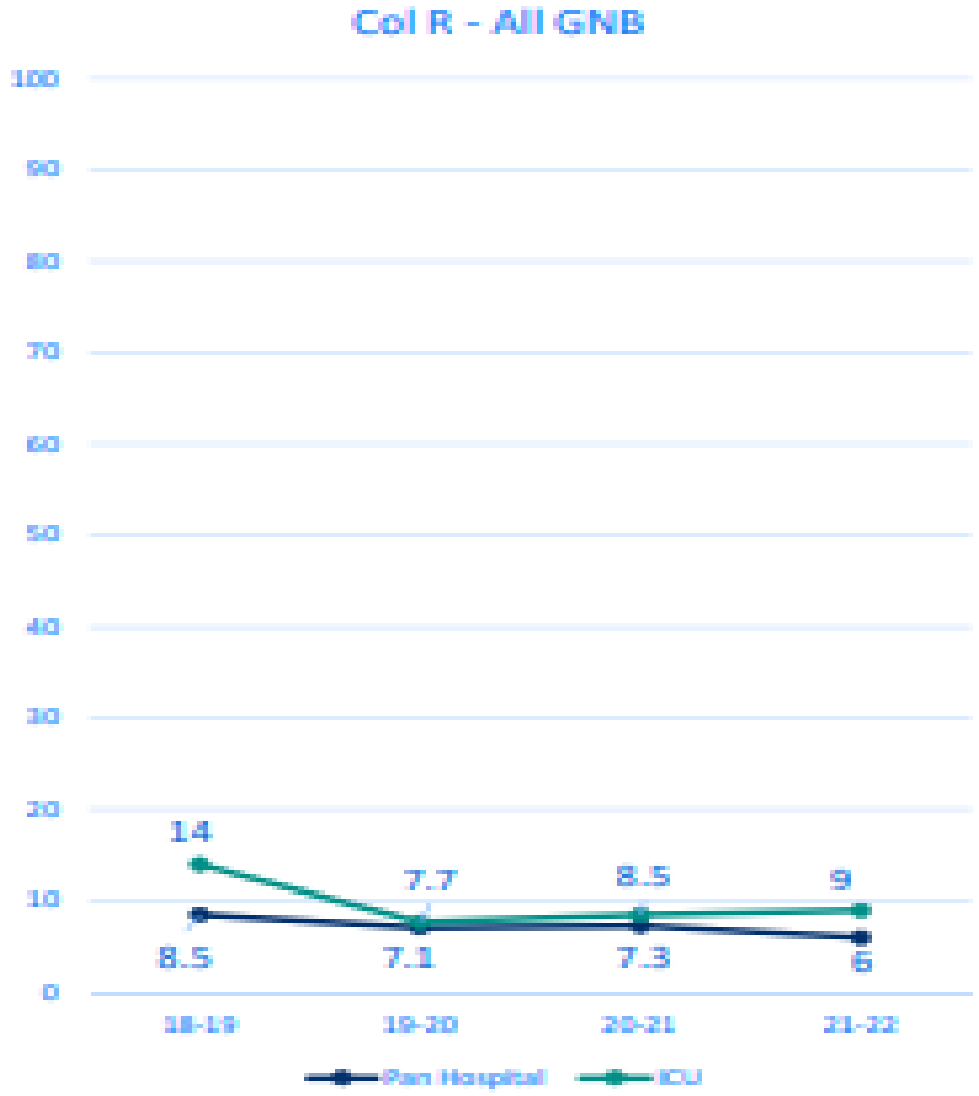
Carbapenem & Colistin Resistance





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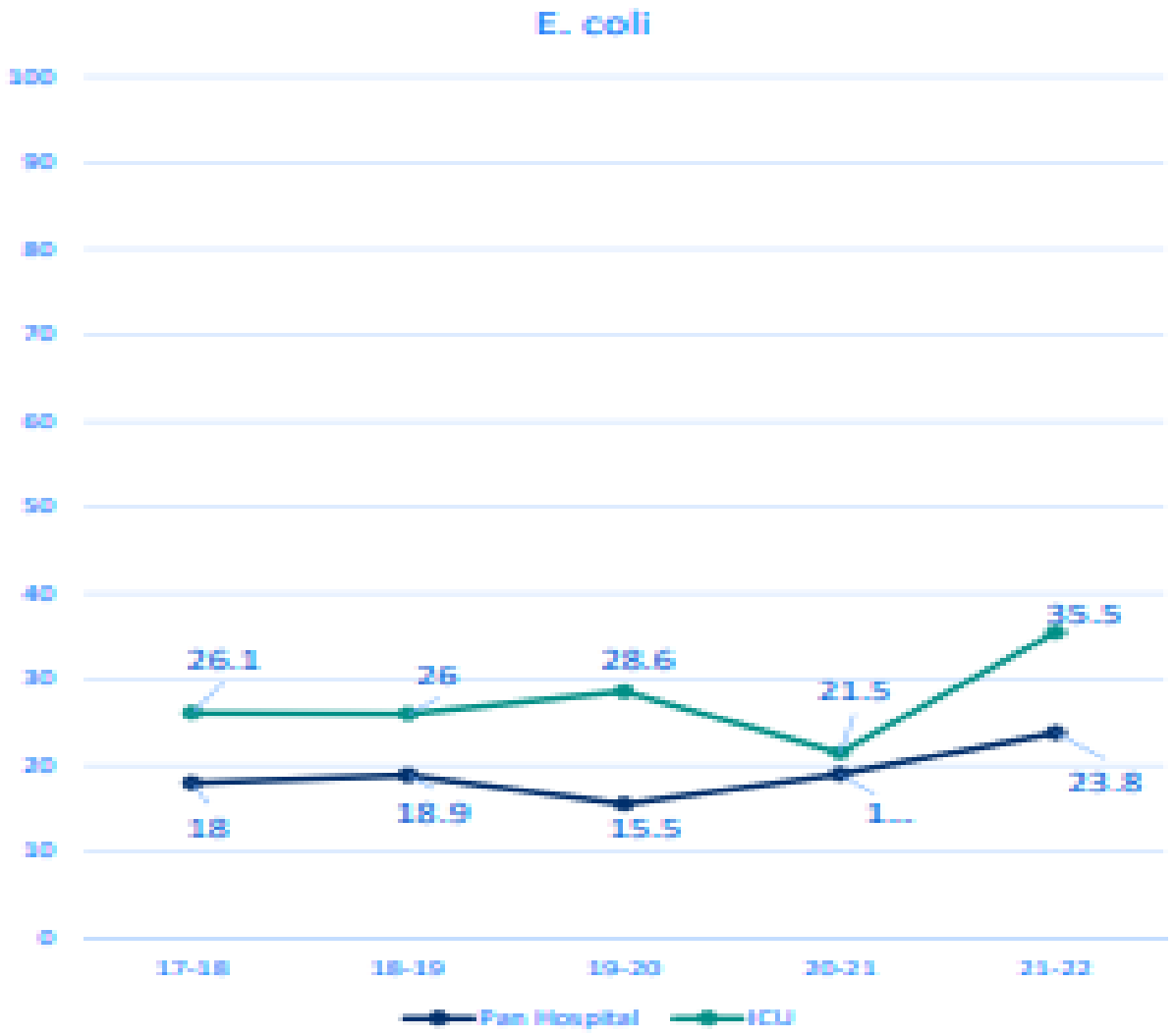
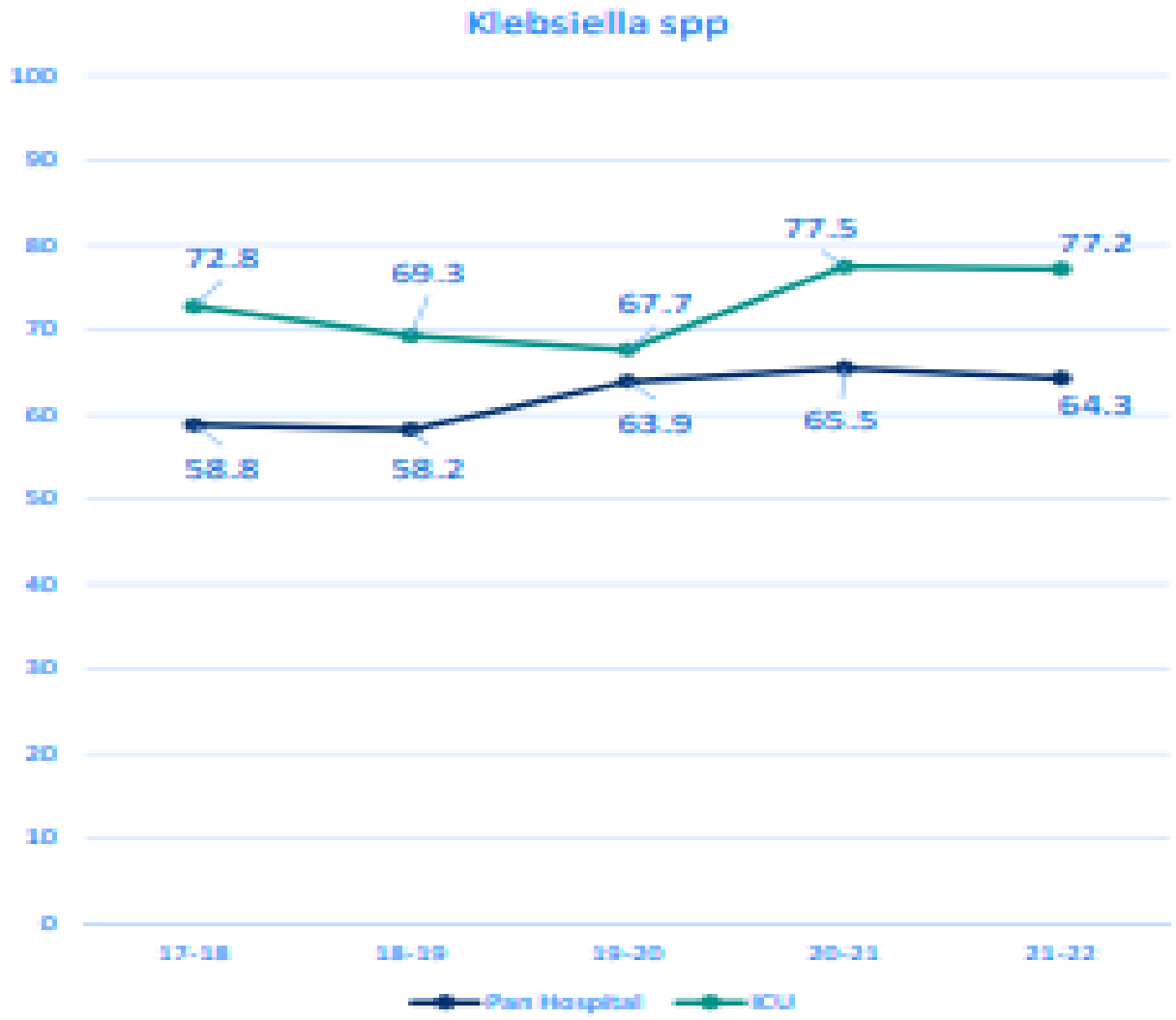
Major Gram Negative Organisms
Carbapenem Resistance





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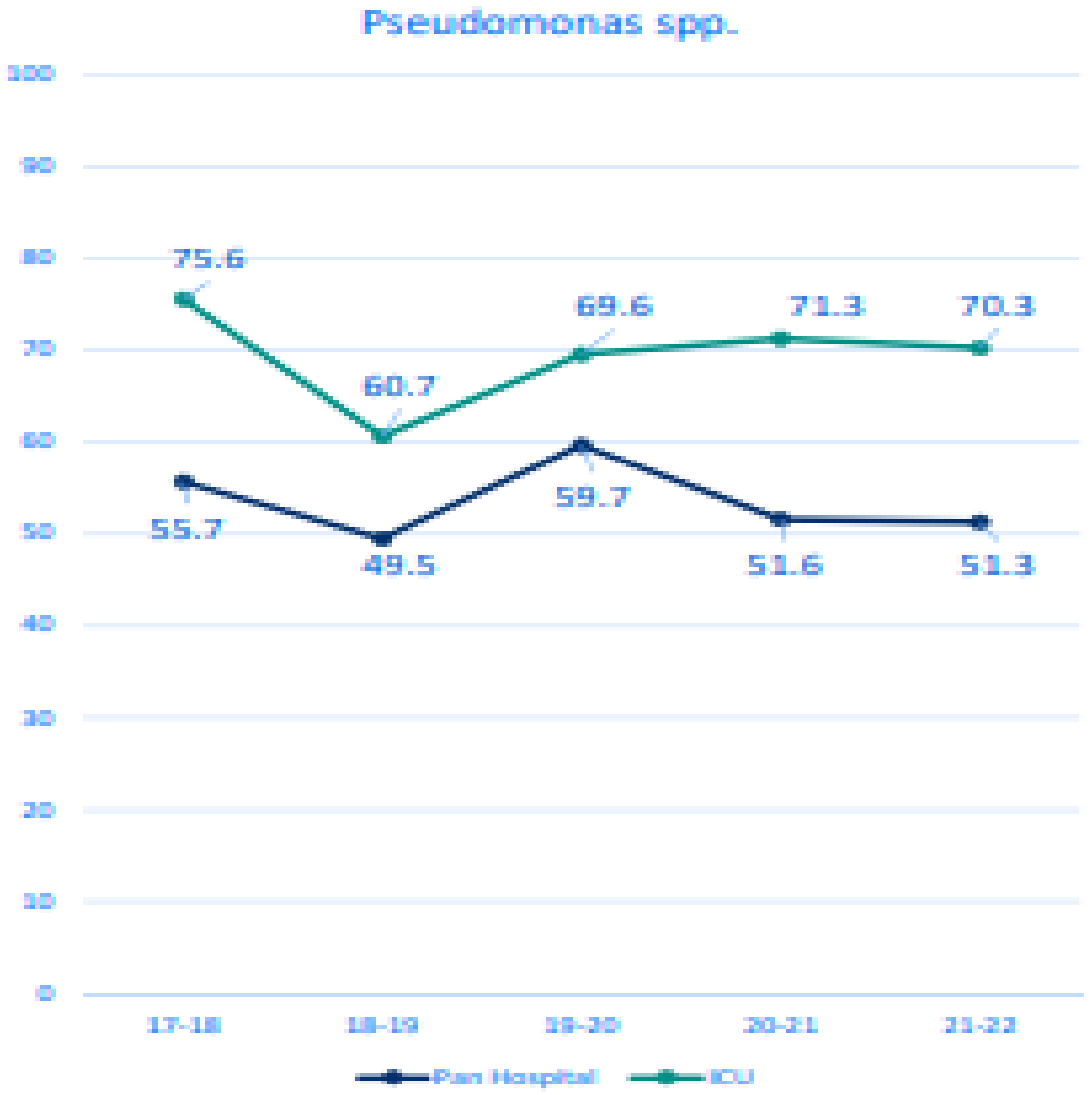
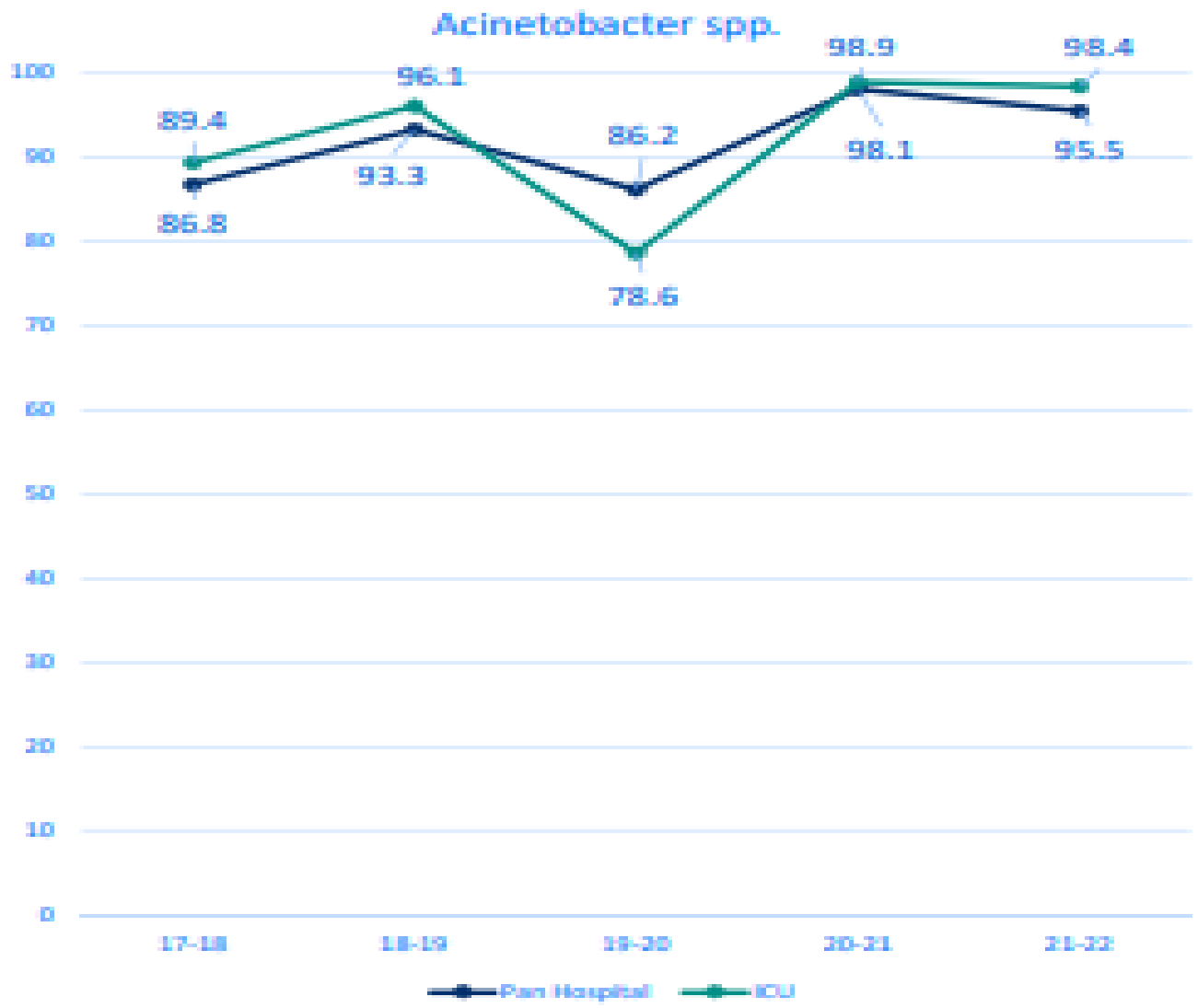
Major Gram Negative Organisms
Carbapenem Resistance





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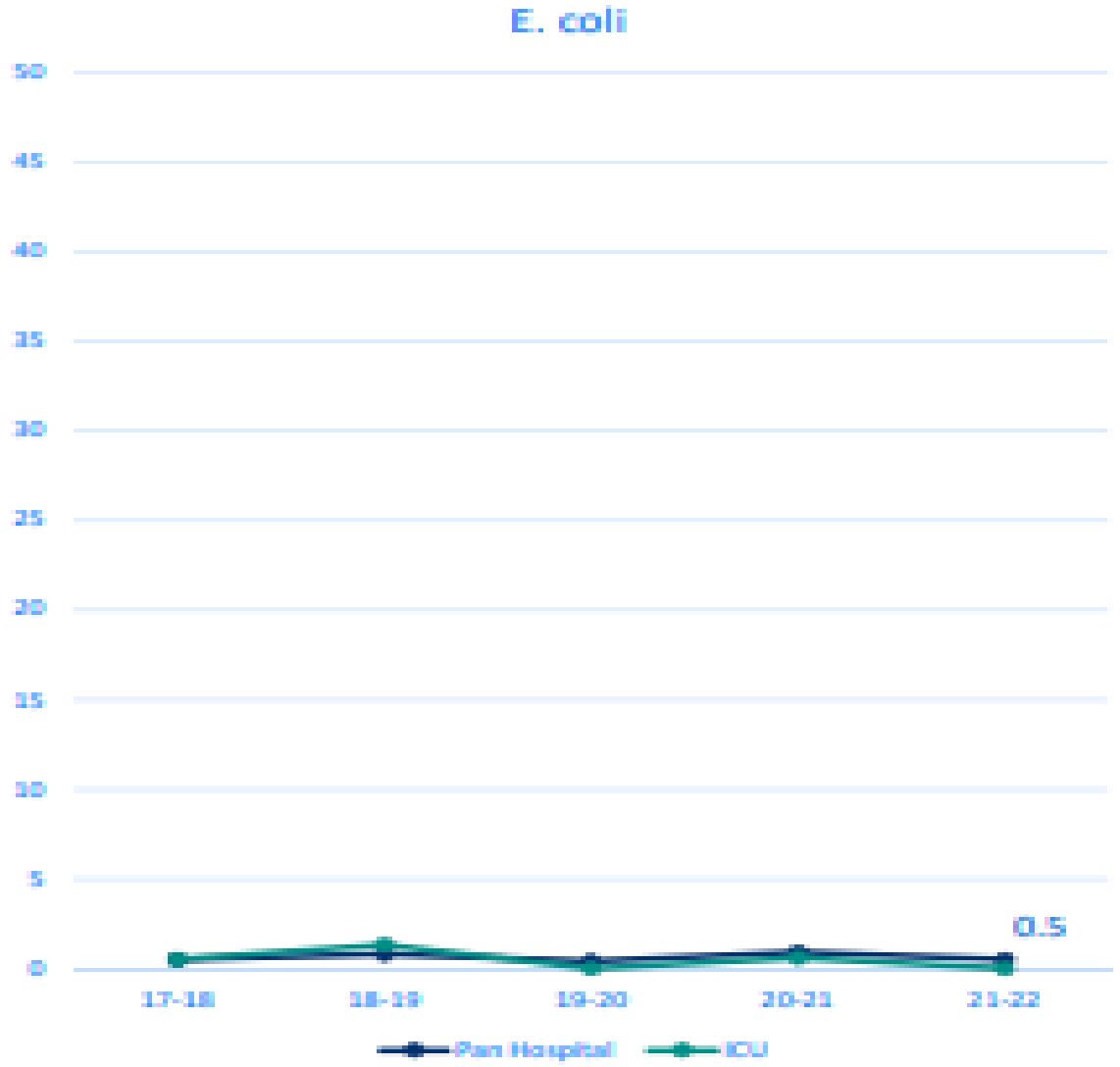
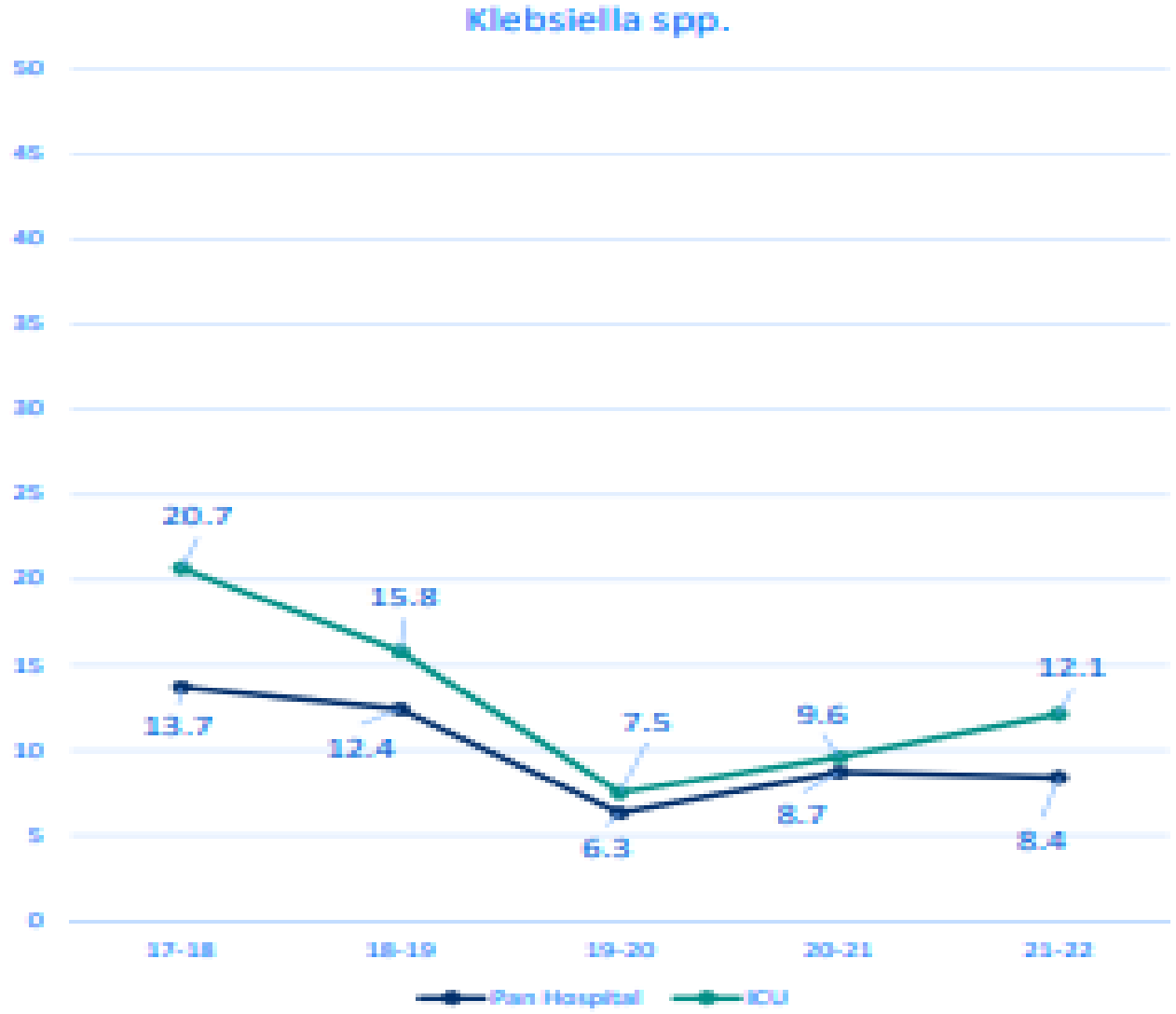
Major Gram Negative Organisms
Colistin Resistance





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Major Gram Negative Organisms
Colistin Resistance

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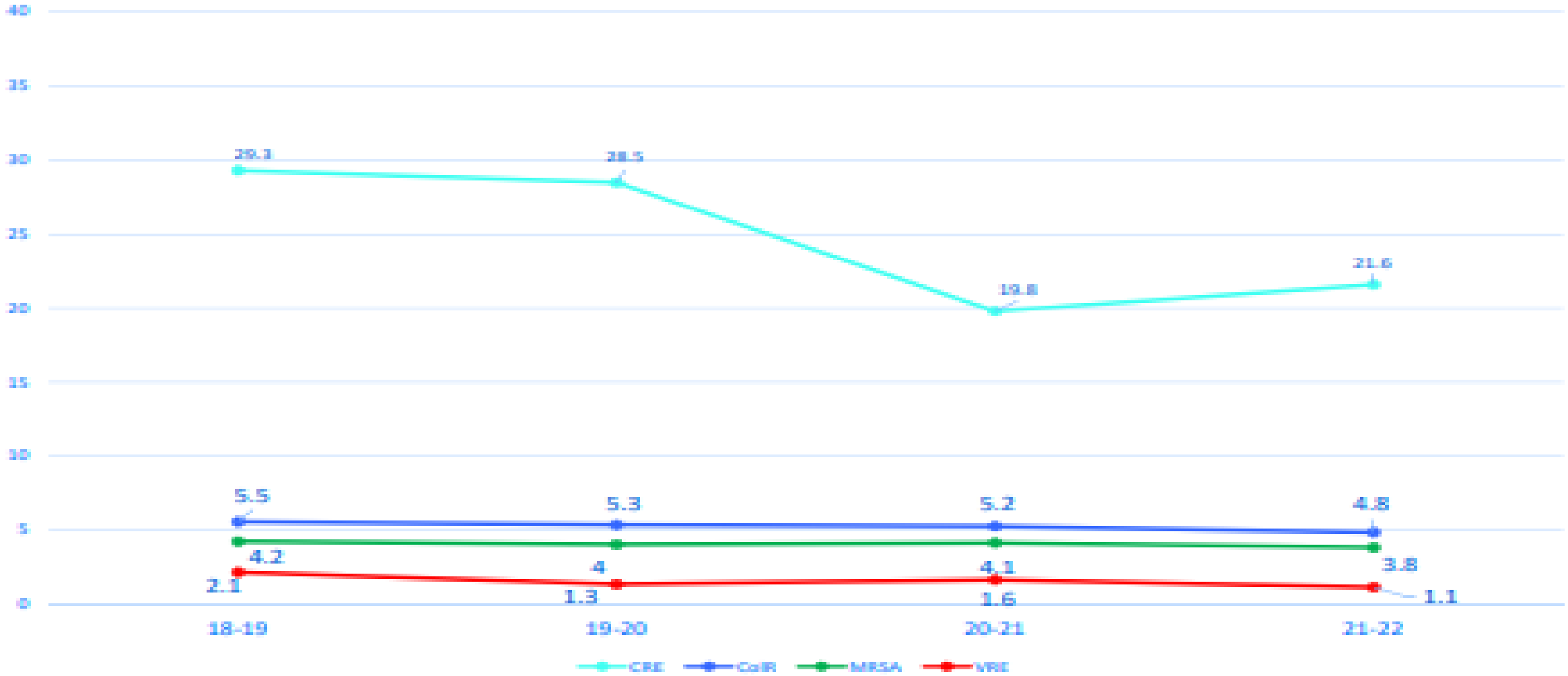
Burden of MDRO



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INDIAN PRIORITY PATHOGEN LIST

CRITICAL PRIORITY	
Enterobacteriaceae *(Klebsiella pneumoniae and Escherichia coli)*	Carbapenem – R Tigecycline – R Colistin – R
Non-fermenting bacteria *(Acinetobacter baumannii and Pseudomonas aeruginosa)*	Carbapenem – R Colistin – R

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INDIAN PRIORITY PATHOGEN LIST

HIGH PRIORITY	
Staphylococcus aureus	MRSA, hVISA Daptomycin – NS Linezolid – R
Enterococcus species	Vancomycin – R Linezolid – R Daptomycin – NS
Salmonella species (Typhoidal and Non-typhoidal)	Azithromycin – NS Third generation cephalosporins – NS Carbapenem – NS

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INDIAN PRIORITY PATHOGEN LIST

MEDIUM PRIORITY	
Streptococcus pneumoniae	Cephalosporin – R Fluoroquinolones – R Linezolid – R
Staphylococcus, coagulase-negative	Vancomycin – R Linezolid – R
Shigella species	Third generation cephalosporins – R Azithromycin – R
Haemophilus influenzae	Third generation cephalosporin – NS Carbapenem – NS
Neisseria meningitidis	Fluoroquinolones – NS Third generation cephalosporins – NS

R: resistant; NS: non-susceptible; MRSA: methicillin-resistant Staph. aureus; hVISA: heterogeneous vancomycin-intermediate Staph. aureus

Mycobacteria [including *Mycobacterium tuberculosis*] were not included in this prioritization exercise as it is a well-established global and national priority for which innovative new treatments are urgently needed and being developed.

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WAY FORWARD!!

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RIGHT TECHNIQUE FOR BLOOD CULTURE SAMPLE COLLECTION

- Clean skin with 2% Chlorhexidine/ 70% isopropyl alcohol (NOT Povidine iodine) for 30 seconds
- Obtain 2 paired cultures (Diagnostic yield raises from 65% to approx. 91%)
- 10ml in each culture bottle (Diagnostic yield increases 1% /ml of blood inoculated)
- Venous and arterial sample has almost same yield
- Take one sample in anaerobic culture media

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ORIGINAL RESEARCH CRITICAL CARE MEDICINE | VOLUME 136, ISSUE 5, P1237-1248, NOVEMBER 01, 2009

Initiation of Inappropriate Antimicrobial Therapy Results in a Fivefold Reduction of Survival in Human Septic Shock

Anand Kumar, MD • Paul Ellis, MD • Yaseen Arabi, MD, FCCP • ... Muhammad Ahsan, MD • Dan Chateau, PhD the Cooperative Antimicrobial Therapy of Septic Shock Database Research Group * •
Show all authors • Show footnotes

DOI: https://doi.org/10.1378/chest.09-0087

Objective

Our goal was to determine the impact of the initiation of inappropriate antimicrobial therapy on survival to hospital discharge of patients with septic shock.

Methods

The appropriateness of initial antimicrobial therapy, the clinical infection site, and relevant pathogens were retrospectively determined for 5,715 patients with septic shock in three countries.

Results

Therapy with appropriate antimicrobial agents was initiated in 80.1% of cases. Overall, the survival rate was 43.7%. There were marked differences in the distribution of comorbidities, clinical infections, and pathogens in patients who received appropriate and inappropriate initial antimicrobial therapy ($p < 0.0001$ for each). The survival rates after appropriate and inappropriate initial therapy were 52.0% and 10.3%, respectively (odds ratio [OR], 9.45; 95% CI, 7.74 to 11.54; $p < 0.0001$). Similar differences in survival were seen in all major epidemiologic, clinical, and organism subgroups. The decrease in survival with inappropriate initial therapy ranged from 2.3-fold for pneumococcal infection to 17.6-fold with primary bacteremia. After adjustment for acute physiology and chronic health evaluation II score, comorbidities, hospital site, and other potential risk factors, the inappropriateness of initial antimicrobial therapy remained most highly associated with risk of death (OR, 8.99; 95% CI, 6.60 to 12.23).

Conclusions

Inappropriate initial antimicrobial therapy for septic shock occurs in about 20% of patients and is associated with a fivefold reduction in survival. Efforts to increase the frequency of the appropriateness of initial antimicrobial therapy must be central to efforts to reduce the mortality of patients with septic shock.

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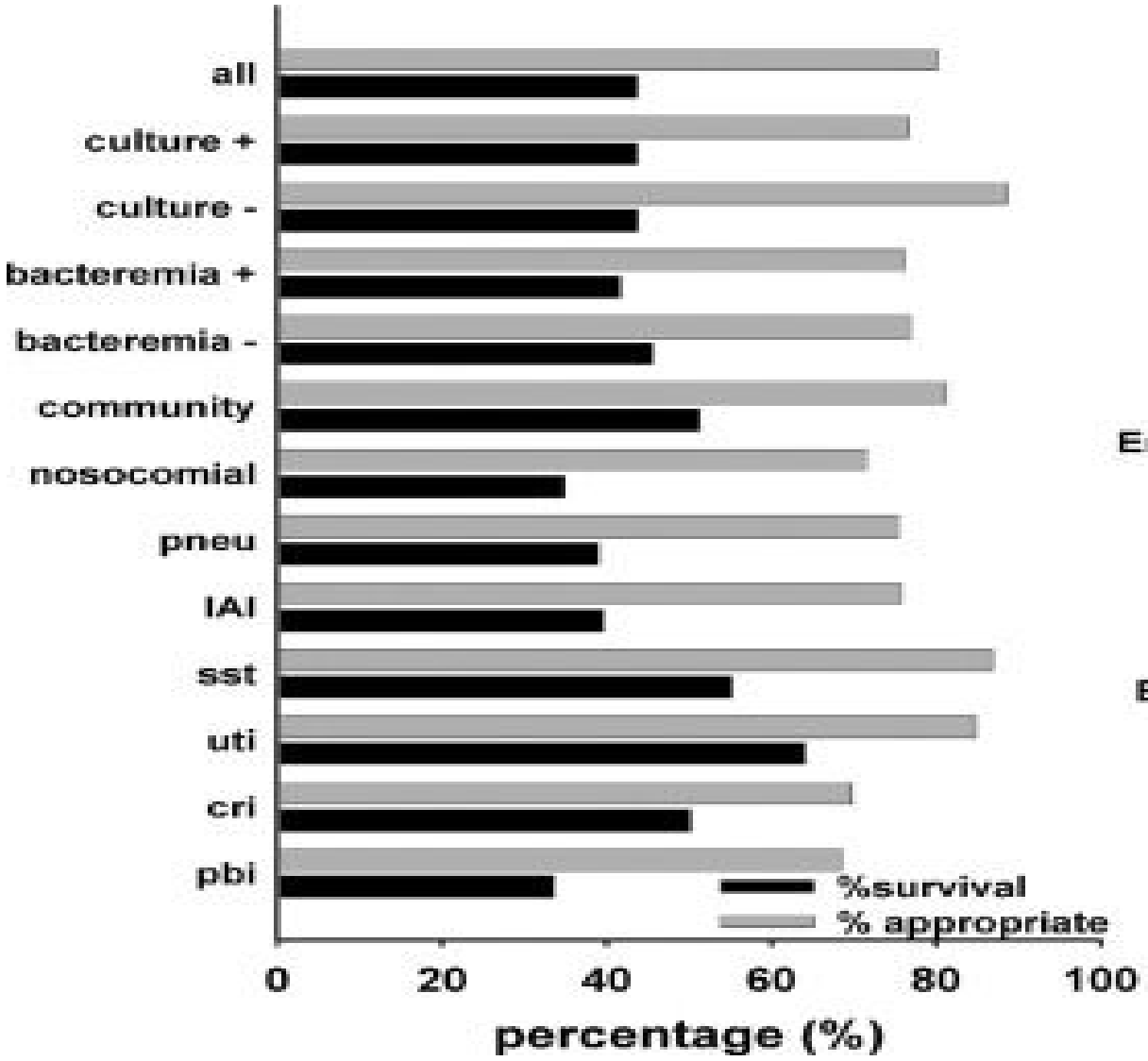
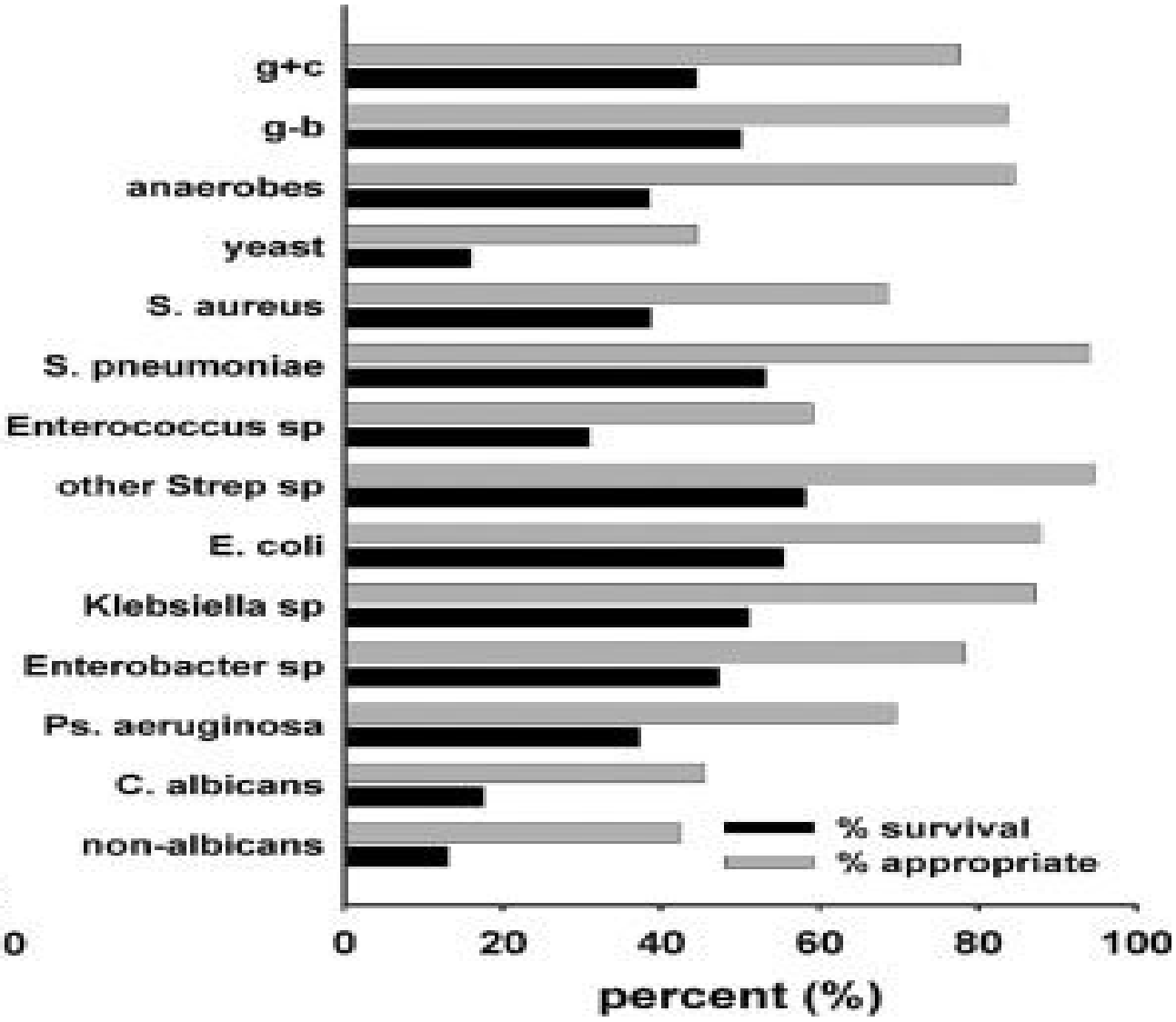
SURVIVAL BENEFIT WITH APPROPRIATE ANTIBIOTIC THERAPY





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COMMON PITFALLS IN DOSING

- Loading dose is irrespective of renal or hepatic status.
- The duration of therapy should not differ for infections caused by organisms with resistant compared to infections caused by more susceptible phenotypes.
- Bactericidal vs bacteriostatic antibiotics work almost the same in *vivo*.
- Delay or absent source containment.
- Errors in Antibiotic dosing.

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TIME DEPENDENT vs CONCENTRATION DEPENDENT KILLING

Concentration-dependent	Time-dependent	Co-dependent
Aminoglycosides	Beta-lactams	Beta-lactams*
Fluoroquinolones	Macrolides (except azithromycin)	Fluoroquinolones
Metronidazole (vs. anaerobes)	Clindamycin	Glycopeptides
	Vancomycin	

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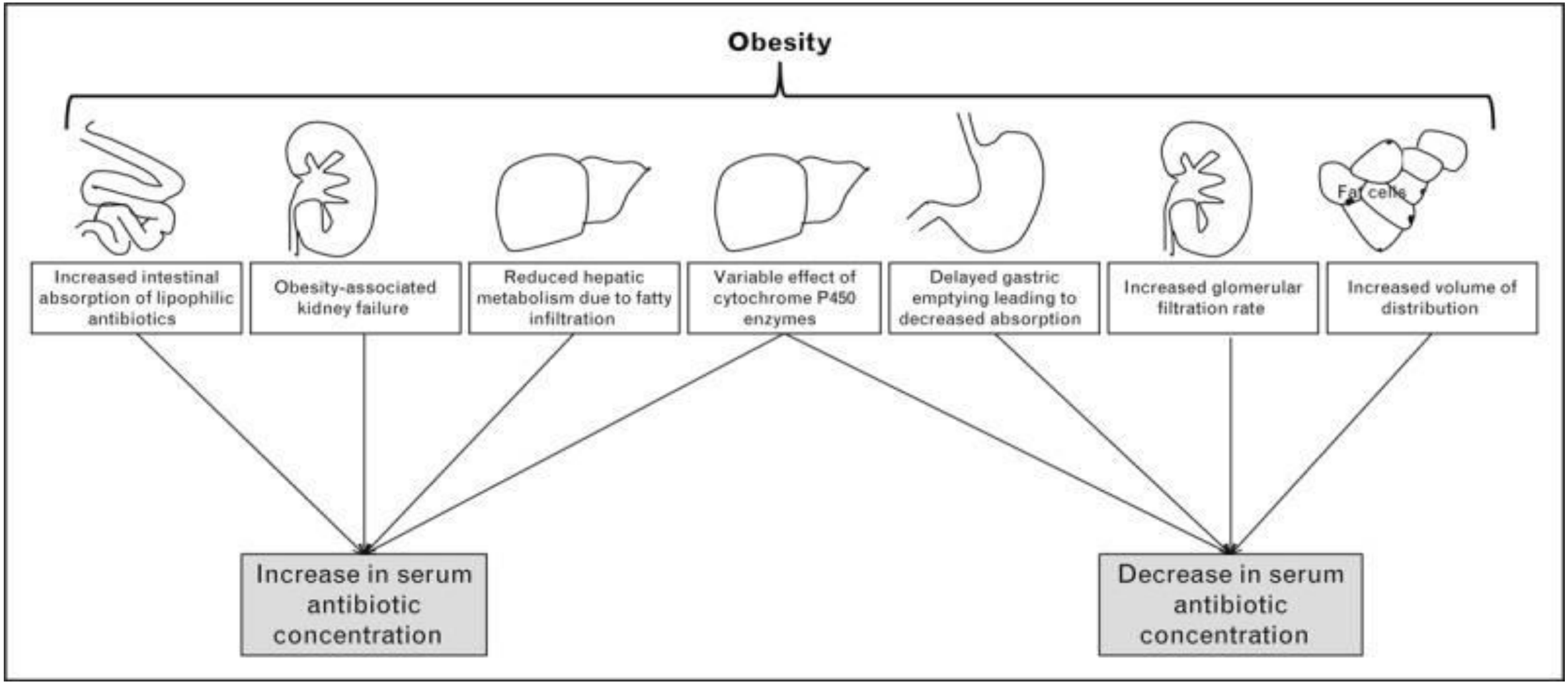
OBESITY AND PK PD OF ANTIMICROBIALS



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WEIGHT ADJUSTED ANTIBIOTIC DOSING

REVIEW ARTICLES

Antimicrobial Dosing in Obese Patients

Rebecca Wurtz, Gail Itokazu, and Keith Rodvold

From the Department of Medicine, Evanston Hospital, Evanston; and the Department of Medicine, Northwestern University Medical School, Cook County Hospital, and University of Illinois at Chicago College of Pharmacy, Chicago, Illinois

Although the dose of some drugs is commonly adjusted for weight, weight-related dosage adjustments are rarely made for most antimicrobials. We reviewed the English-language literature on antimicrobial pharmacokinetics and dosing in obesity. Although there are many potential pharmacokinetic consequences of obesity, the actual effect on the pharmacokinetics and clinical efficacy of most antimicrobials is unknown. Since ~30% of adipose is water, an empirical approach is use of the Devine formula to calculate ideal body weight (IBW), to which is added a dosing weight correction factor (DWCF) of 0.3 times the difference between actual body weight (ABW) and IBW (IBW + 0.3 × [ABW-IBW]) to arrive at a weight on which to base dosage of hydrophilic antibiotics. No studies confirm this approach for β-lactam drugs. Clinical studies suggest a DWCF of ~0.40 for aminoglycosides and 0.45 for quinolones. Final dosage adjustments for antimicrobials with a narrow toxic-therapeutic window should be based on serum concentrations.

Although the dose of some medications—including cancer chemotherapeutic agents, anesthetics, and more recently heparin [1–9]—is commonly adjusted for weight, weight-related dosage adjustments for antimicrobials are rarely made. Distribution, metabolism, and clearance of many drugs are altered by physiological changes associated with obesity (table 1).

Ideal Body Weight, Obesity, Body Surface Area, and Body Mass Index

Equations to calculate IBWs for men and women are given in table 2 (curiously, the equations mix metric and standard measures) [10–12]. The commonly used Devine formula [10] defines IBW for men as 50 kg plus 2.3 times the height in

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Type of antimicrobial	Weight for calculating dose	Reference
β-Lactam drug	Empirical: IBW + 0.3(ABW-IBW)	. . .*
Aminoglycoside		
Gentamicin	IBW + 0.43(ABW-IBW)	[21]
Tobramycin	IBW + 0.58(ABW-IBW)	[57]
For children	IBW + 0.40(ABW-IBW)	[58]
Amikacin	IBW + 0.38(ABW-IBW)	[59]
Vancomycin	ABW	[60]
Sulfonamide	IBW†	[61]
Quinolone		
Ciprofloxacin	IBW + 0.45(ABW-IBW)	[62, 63]
Macrolide	IBW	[64]
Mycobacterial	IBW	[65] (single case report)
Antifungal		
Amphotericin	Empirical: ABW	. . .*
Flucytosine	IBW	[66] (single case report)
Fluconazole	6 mg/kg qd	[67]
Antiviral		
Acyclovir	IBW	[68]
Zidovudine	ABW	[69] (2 case reports of pregnant women)

NOTE. ABW = actual body weight; IBW = ideal body weight.
* No clinical studies confirm this approach.
† May vary for different sulfonamides.

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COMMON PITFALLS IN ANTIBIOTIC SELECTION

- Use of Vancomycin in MSSA
- Use of Fosfomycin or Nitrofurantoin in Pyelonephritis
- Fosfomycin should be avoided for prostatitis caused by Gram-negative organisms other than E. coli because of *fos*A gene
- Use Polymyxin B in non urinary tract infection and Colistin in urinary tract sepsis
- In case of ESBL use carbapenems even though susceptibility to non beta lactam antibiotics is demonstrated(e.g., ciprofloxacin, trimethoprim-sulfamethoxazole, gentamicin).
- Routine addition of nebulized antibiotics for the treatment of respiratory infections caused by DTR-P. aeruginosa.

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PRECISION MEDICINE AND ROLE OF RAPID MOLECULAR ASSAY

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RAPID DIAGNOSTIC ASSAY- BIOFIRE BCID2 PANEL

- The IDSA recommends the addition of rapid diagnostic testing to an effective Antimicrobial Stewardship Program.
- Tests for 43 targets associated with bloodstream infections, including gram-negative bacteria, gram-positive bacteria, yeast, and 10 antimicrobial resistance genes
- All with one test and with results available in about an hour from positive blood culture.
- Combined with antimicrobial stewardship, achieved >$3,000 per patient in overall hospital savings
- The BioFire BCID Panel + antimicrobial stewardship interventions decreased time to optimal therapy by 33.5 hours

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ADVANTAGES OF BCID2 PANEL TURN AROUND TIME

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BIOFIRE BCID2 PANEL REPORT

FilmArray® BCID Panel

BIOFIRE

www.BioFireDx.com

Run Summary			
Sample ID:		Run Date:	
Organisms Detected:	*Neisseria meningitidis*	Controls:	Passed
Applicable Antimicrobial Resistance Genes:			

Result Summary - Interpretations	
Antimicrobial Resistance Genes	
⊘ N/A	KPC (carbapenem-resistance gene)
⊘ N/A	*mecA* (methicillin-resistance gene)
⊘ N/A	*vanA/B* (vancomycin-resistance genes)
⚠ **NOTE:** Antimicrobial resistance can occur via multiple mechanisms. A Not Detected result for the FilmArray antimicrobial resistance gene assays does not indicate antimicrobial susceptibility. Subculturing is required for species identification and susceptibility testing of isolates.	
Gram Positive Bacteria	
Not Detected	*Enterococcus*
Not Detected	*Listeria monocytogenes*
Not Detected	*Staphylococcus*
Not Detected	*Staphylococcus aureus*
Not Detected	*Streptococcus*
Not Detected	*Streptococcus agalactiae* (Group B)
Not Detected	*Streptococcus pneumoniae*
Not Detected	*Streptococcus pyogenes* (Group A)
Gram Negative Bacteria	
Not Detected	*Acinetobacter baumannii*
Not Detected	*Enterobacteriaceae*
Not Detected	*Enterobacter cloacae* complex
Not Detected	*Escherichia coli*
Not Detected	*Klebsiella oxytoca*
Not Detected	*Klebsiella pneumoniae*
Not Detected	*Proteus*
Not Detected	*Serratia marcescens*
Not Detected	*Haemophilus influenzae*
✓ Detected	*Neisseria meningitidis*
Not Detected	*Pseudomonas aeruginosa*
Yeast	
Not Detected	*Candida albicans*
Not Detected	*Candida glabrata*
Not Detected	*Candida krusei*
Not Detected	*Candida parapsilosis*
Not Detected	*Candida tropicalis*

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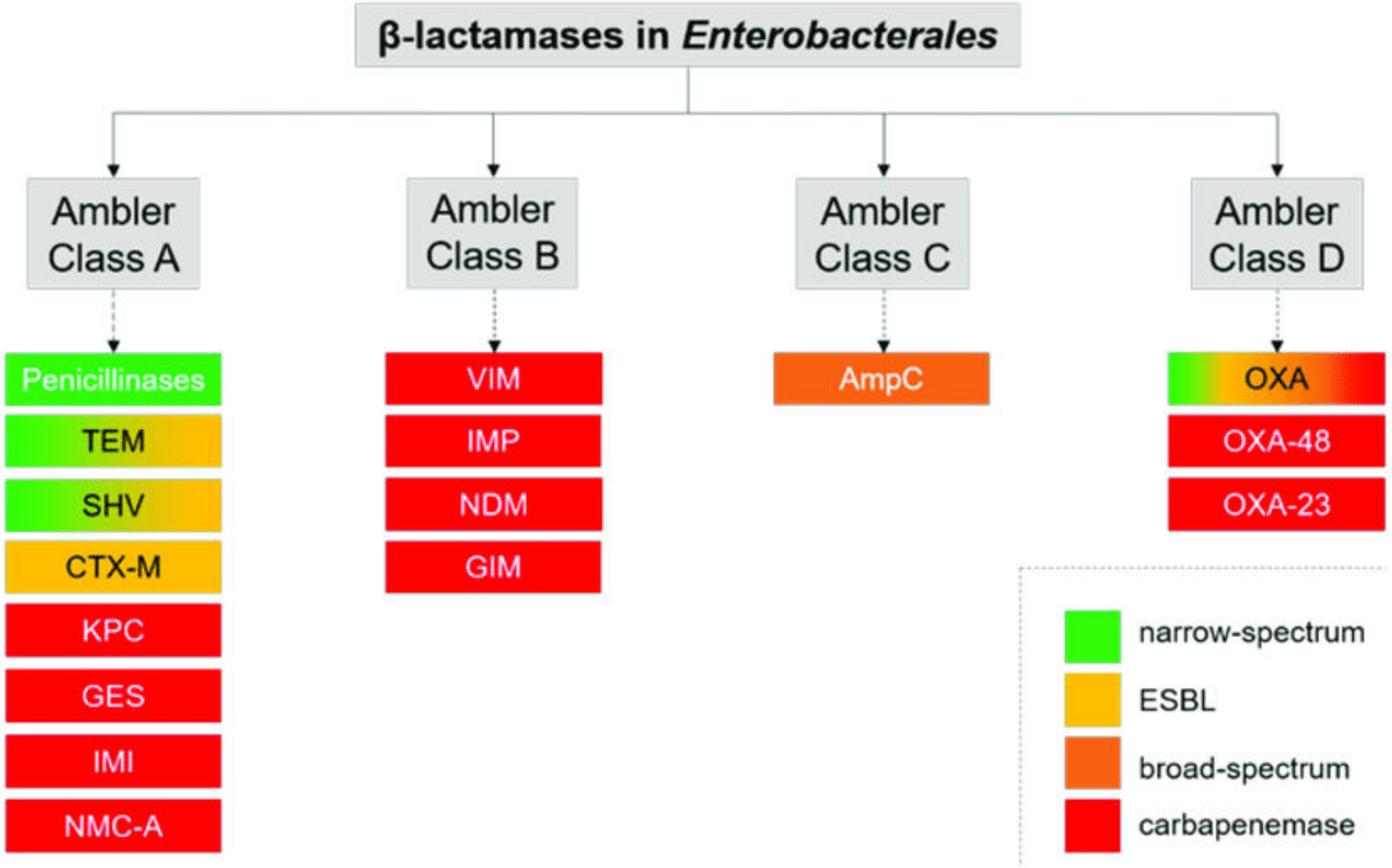

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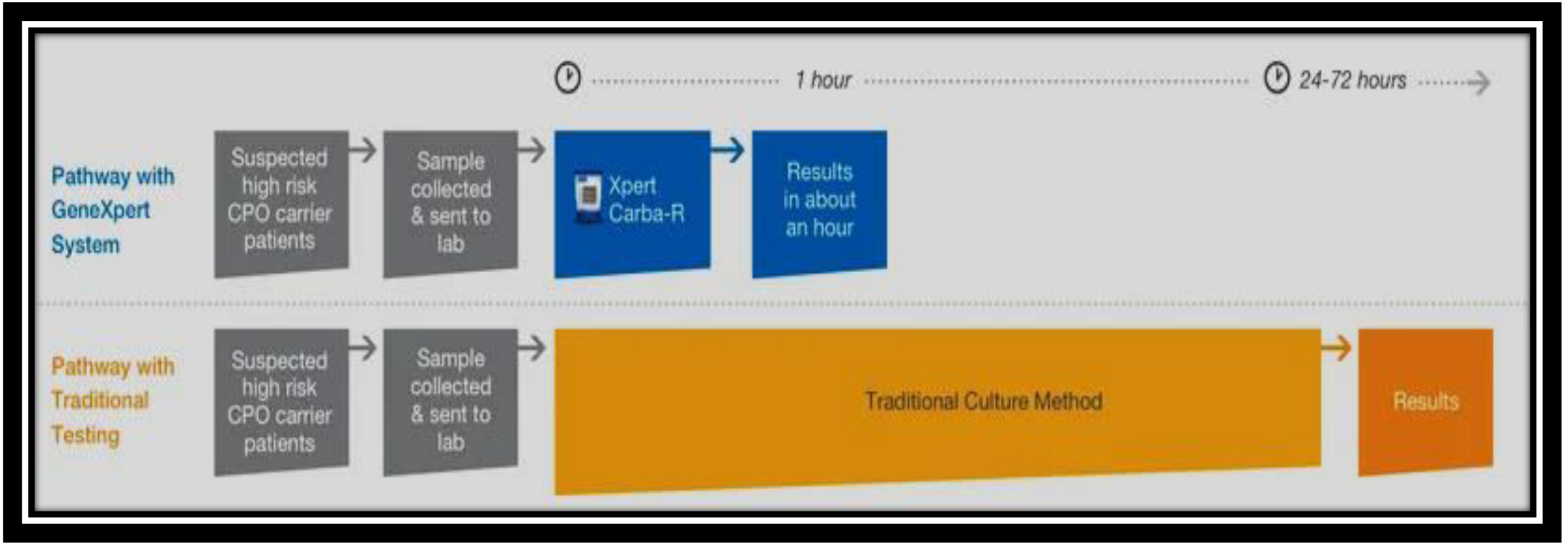
XPERT CARBA-R TEST

Xpert Carba-R is an on-demand PCR test that detects and differentiates the most prevalent carbapenemases gene families (KPC, NDM, VIM, IMP-1 and OXA-48, now covering OXA-181 & OXA-232) in 50-60 minutes.



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TREATMENT OPTIONS FOR CARBAPENEMASES PRODUCING ORGANISMS

- KPC- Meropenem-vaborbactam /ceftazidime-avibactam/ imipenem-cilastatin-relebactam
- NDM and other metallo-β-lactamase-producers - Ceftazidime-avibactam + aztreonam / cefiderocol as monotherapy
- OXA-48- Ceftazidime-avibactam

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Laboratory Investigation Report

Patient Name	: Mr.	Centre	: 1566 - Blk Superspeciality Hospital
Age/Gender	: 85 Y 1 M 15 D /M	OP/IP No/UHID	611 A/
MaxID/Lab ID	:	Collection Date/Time	: 01/Dec/2022 11:46AM
Ref Doctor	: Dr Avinash	Reporting Date/Time	: 01/Dec/2022 02:27PM

SIN No:BCIP1078622

Microbiology

Test Name	Result	Unit	Bio Ref Interval

Carba-Resistant gene detection, RT PCR (Xpert)
Real Time PCR Assay

Sample Type	Bacterial growth
Source	Sin.no- 10043265
Carba-Resistant Gram Negative Bacilli	Klebsiella pneumoniae
IMP1	Not Detected
VIM	Not Detected
NDM	Detected
KPC	Not Detected
OXA - 48	Detected

Note:

1. This is a qualitative in-vitro diagnostic test for detection and differentiation of the following gene sequences associated with carbapenem-non-susceptibility - Imipenemase (IMP), Verona Integron-mediated Metallo-beta-lactamase (VIM), New Delhi Metallo-beta-lactamase (NDM), Klebsiella pneumoniae Carbapenemase (KPC) and Class D Oxacillinase (OXA-48).

2. Mechanisms of resistance to carbapenems other than the above mentioned enzymes can not be detected by this assay.

3. IMP-7, IMP-13 & IMP-14 gene sequences will generate a negative IMP result.

4. Mutations or polymorphisms in primer or probe binding regions may affect detection of current, new or unknown variants resulting in false negative results.

*This test is not under the scope of NABL accreditation

Kindly correlate with clinical findings

*** End Of Report ***

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SUMMARY

- Two decades of Surviving Sepsis Campaign has brought about significant survival benefits
- Raise of antimicrobial resistance along with non availability of newer antibiotics poses a danger of substantial loss of life.
- Right antibiotic of proper dose through right route with perfect timing is the key for successful treatment of sepsis.
- Newer molecular diagnostic assay helps us save time and cost and also to tailor the antibiotics and doses.

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REFERENCES

- https://www.sccm.org/SurvivingSepsisCampaign/Guidelines/Adult-Patients
- https://www.idsociety.org/practice-guideline/amr-guidance/
- https://www.biofiredx.com/products/the-filmarray-panels/filmarraybcid/
- https://www.cepheid.com/en/tests/Healthcare-Associated-Infections/Xpert-Carba-R

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THANK YOU!