AMS IN THE ICU SETTING

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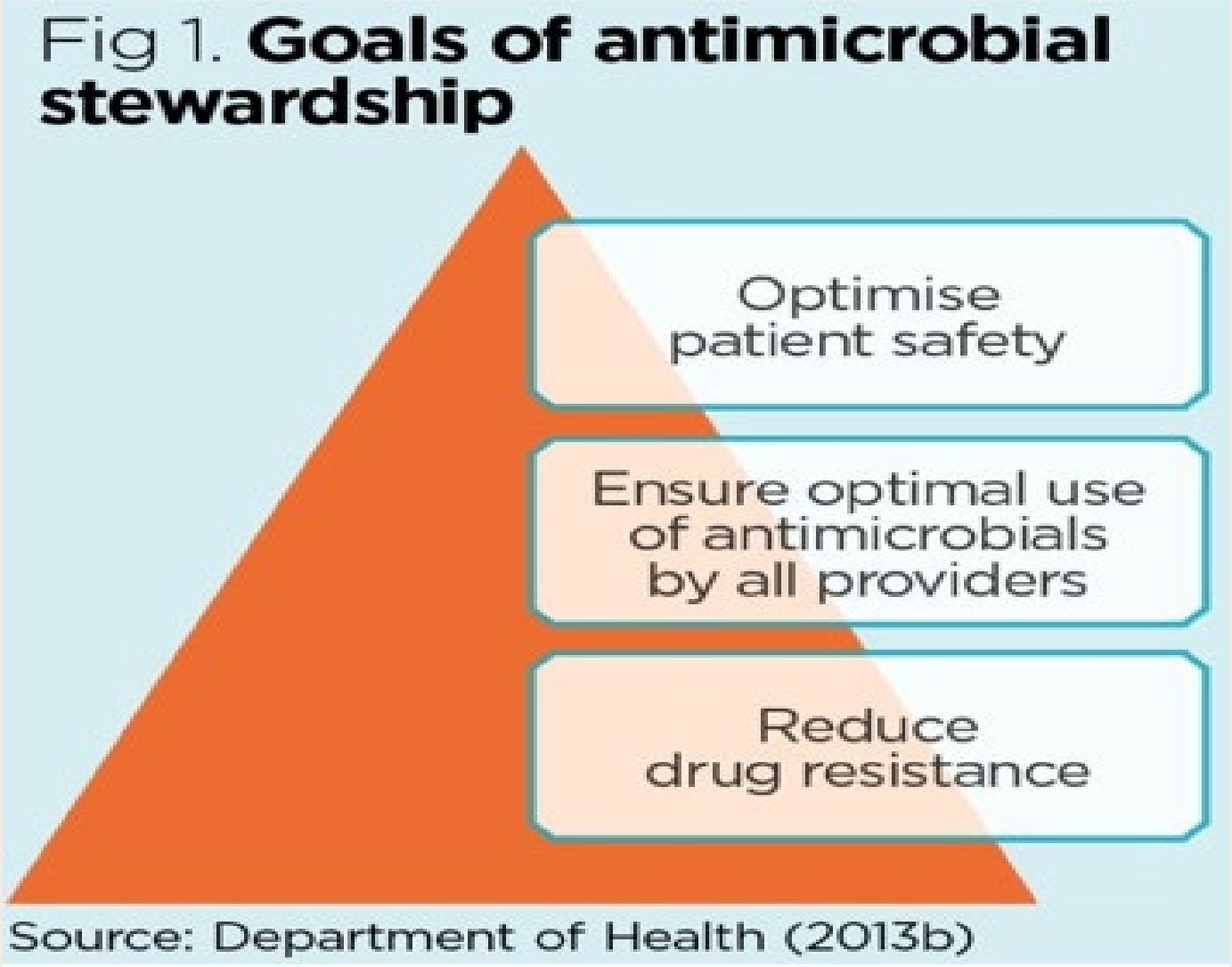
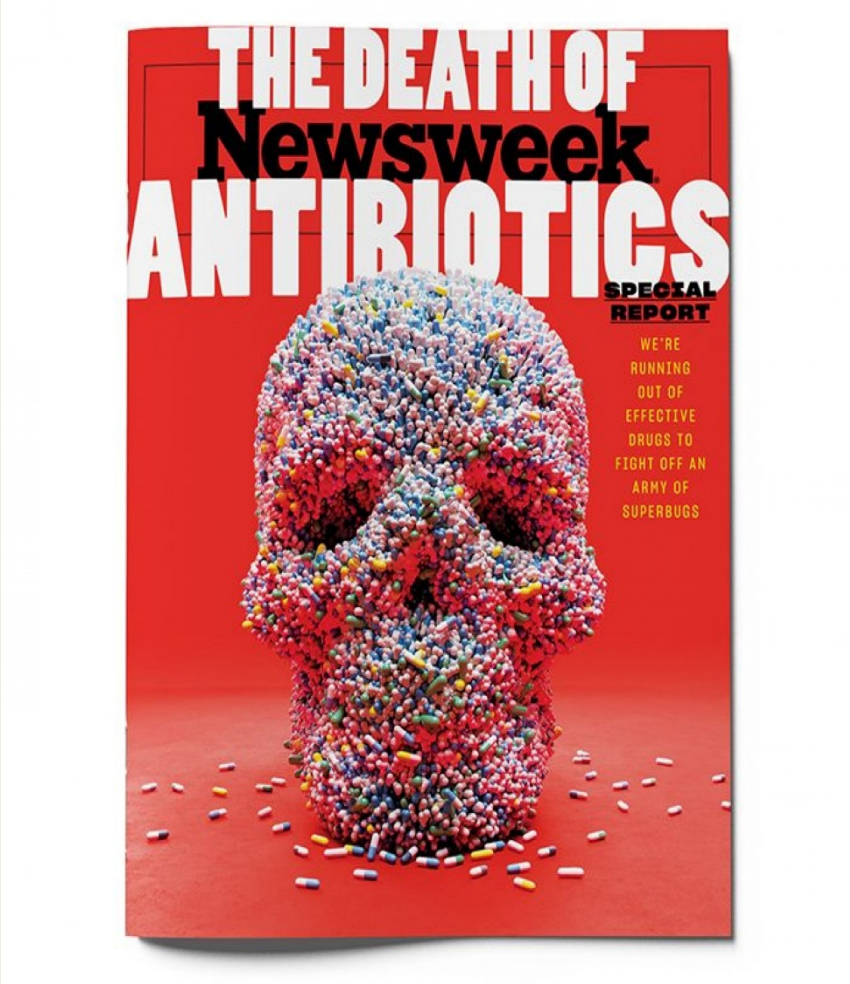


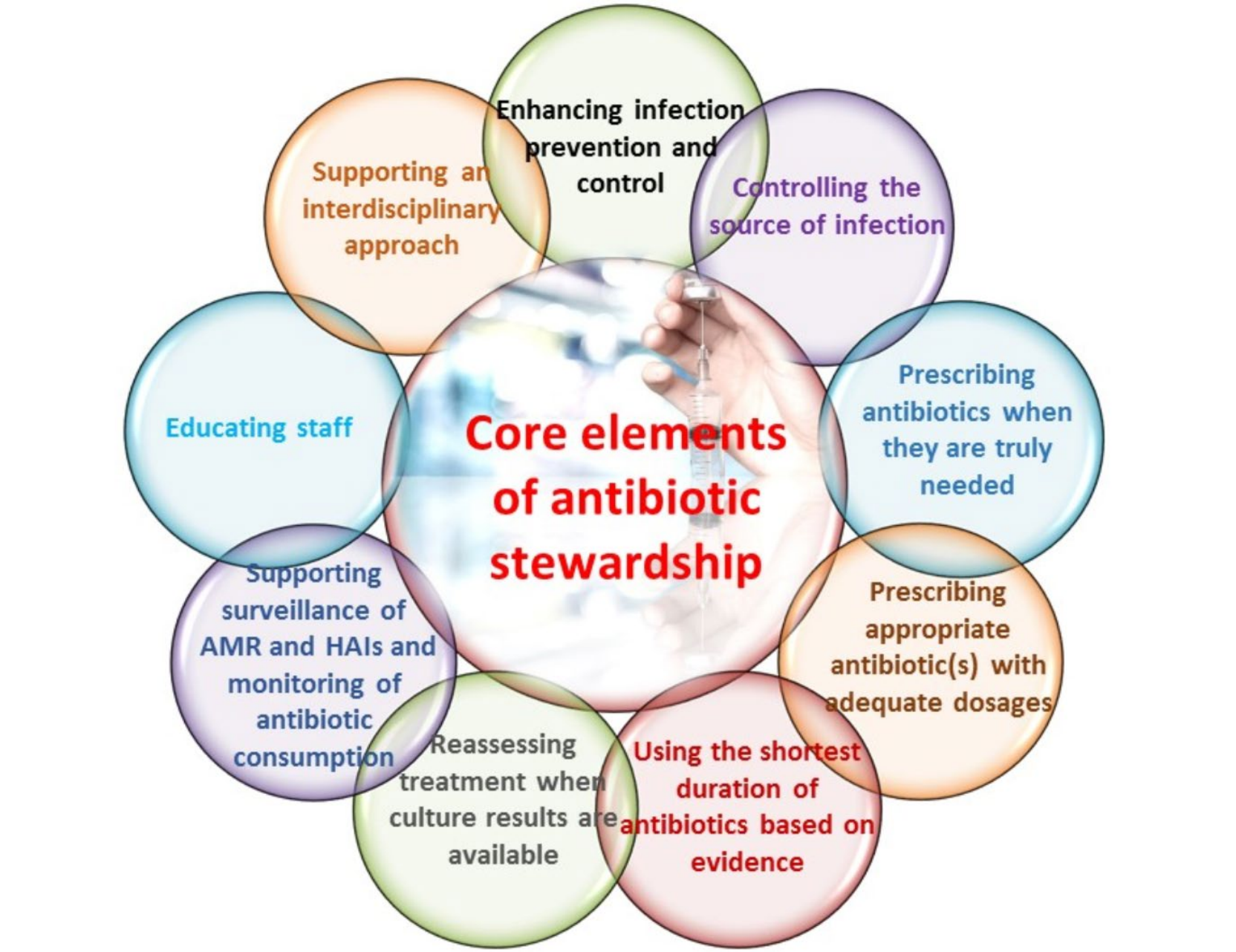
Antimicrobial stewardship programs focus on optimizing the appropriate use of currently available antimicrobial agents with the goals of improving outcomes for patients with infections caused by MDR gram-negative organisms, slowing the progression of antimicrobial resistance, and reducing hospital costs.

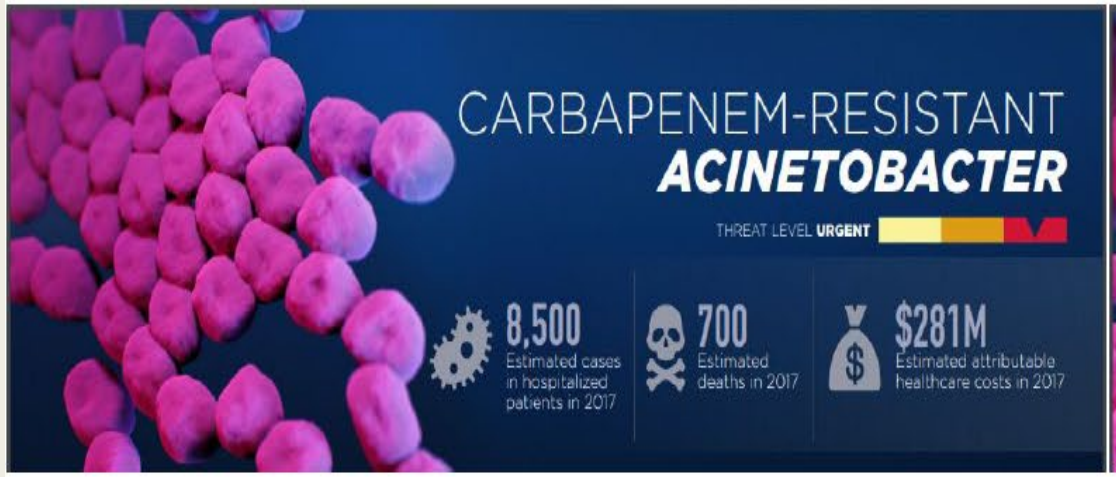
OUTLINE

- Epidemiology and AMR and the ICU
  - *Examples from the region*
- Consequences of AMR in the ICU
- Barriers to successful AMS in the ICU
- Key elements of AMS in the ICU
- Role of Infection Control
- Role of novel diagnostics
- Optimization of antibiotic usage
- Summary

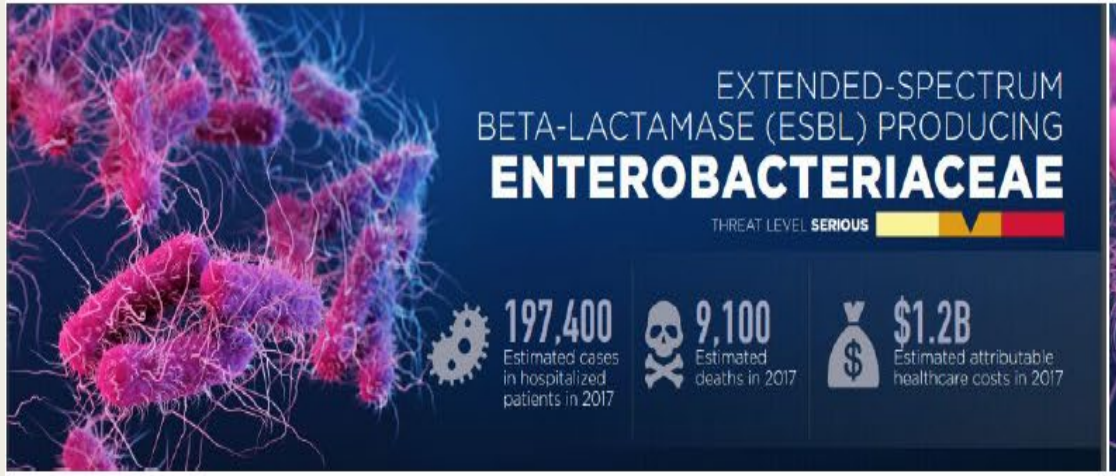
  Call To Action




Core elements of antibiotic stewardship
Enhancing infection prevention and control
Supporting an interdisciplinary approach
Controlling the source of infection
Educating staff
Prescribing antibiotics when they are truly needed
Supporting surveillance of AMR and HAIs and monitoring of antibiotic consumption
Prescribing appropriate antibiotic(s) with adequate dosages
Reassessing treatment when culture results are available
Using the shortest duration of antibiotics based on evidence


CARBAPENEM-RESISTANT
ACINETOBACTER
THREAT LEVEL URGENT
8,500
Estimated cases in hospitalized patients in 2017
700
Estimated deaths in 2017
$281M
Estimated attributable healthcare costs in 2017


CARBAPENEM-RESISTANT
ENTEROBACTERIACEAE
THREAT LEVEL URGENT
13,100
Estimated cases in hospitalized patients in 2017
1,100
Estimated deaths in 2017
$130M
Estimated attributable healthcare costs in 2017

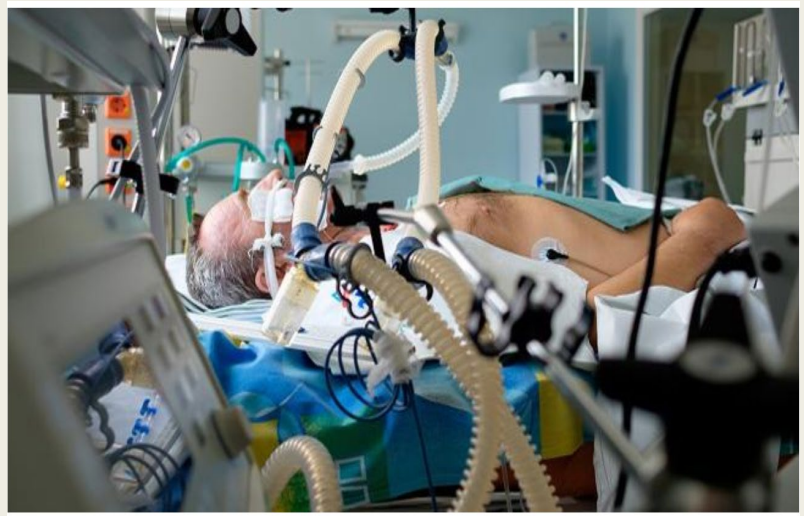

EXTENDED-SPECTRUM
BETA-LACTAMASE (ESBL) PRODUCING
ENTEROBACTERIACEAE
THREAT LEVEL SERIOUS
197,400
Estimated cases in hospitalized patients in 2017
9,100
Estimated deaths in 2017
$1.2B
Estimated attributable healthcare costs in 2017


MULTIDRUG-RESISTANT
PSEUDOMONAS AERUGINOSA
THREAT LEVEL SERIOUS
32,600
Estimated cases in hospitalized patients in 2017
2,700
Estimated deaths in 2017
$767M
Estimated attributable healthcare costs in 2017

AMR in the ICU

- AMR threatens any patient in the hospital

- Patients in the ICU are particularly at risk of acquiring AMR infections due to
  - *Immune deficiencies*
  - *Invasive devices*
  - *Increased risk of transmission*
  - *Exposure to antibiotics*

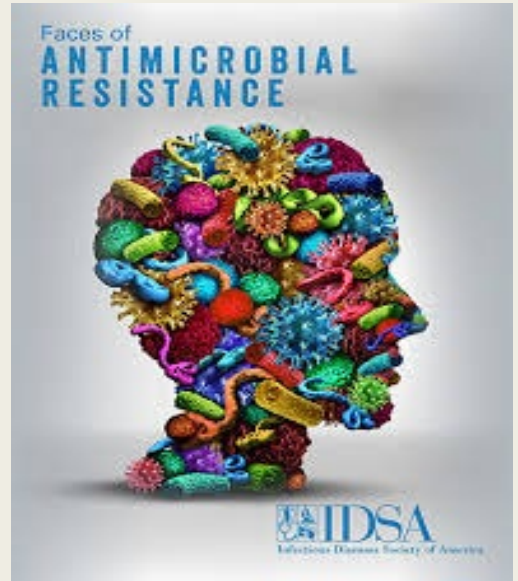


- AMR is present in every ICU globally
  - *prevalence is geographically different*

MacVane SH. Antimicrobial Resistance in the Intensive Care Unit: A Focus on Gram-Negative Bacterial Infections. J Intensive Care Med 2017 Jan;32(1):25-37. Epub 2016 Jan 15.

Epidemiology of AMR in the ICU

- Considerable rise in the prevalence of infections in ICUs
  - ***51%** of ICU patients have an infection (7087 of 13,796)*
  - ***71% of ICU patients are receiving antibiotics***
- **Respiratory tract infections** account **64%** of all infections
- Microbiological culture results were positive in 4947 **(70%)** of the infected patients
  - ***62% gram-negative organisms***
  - ***47% gram-positive organisms***
  - ***19% fungi***



Vincent JL, Rello J, Marshall J, Silva E, Anzueto A, Martin CD, Moreno R, Lipman J, Gomersall C, Sakr Y, Reinhart K, EPIC II Group of Investigators International study of the prevalence and outcomes of infection in intensive care units. JAMA. 2009;302(21):2323

Epidemiology of AMR in the ICU

Common infectious syndromes in the ICU

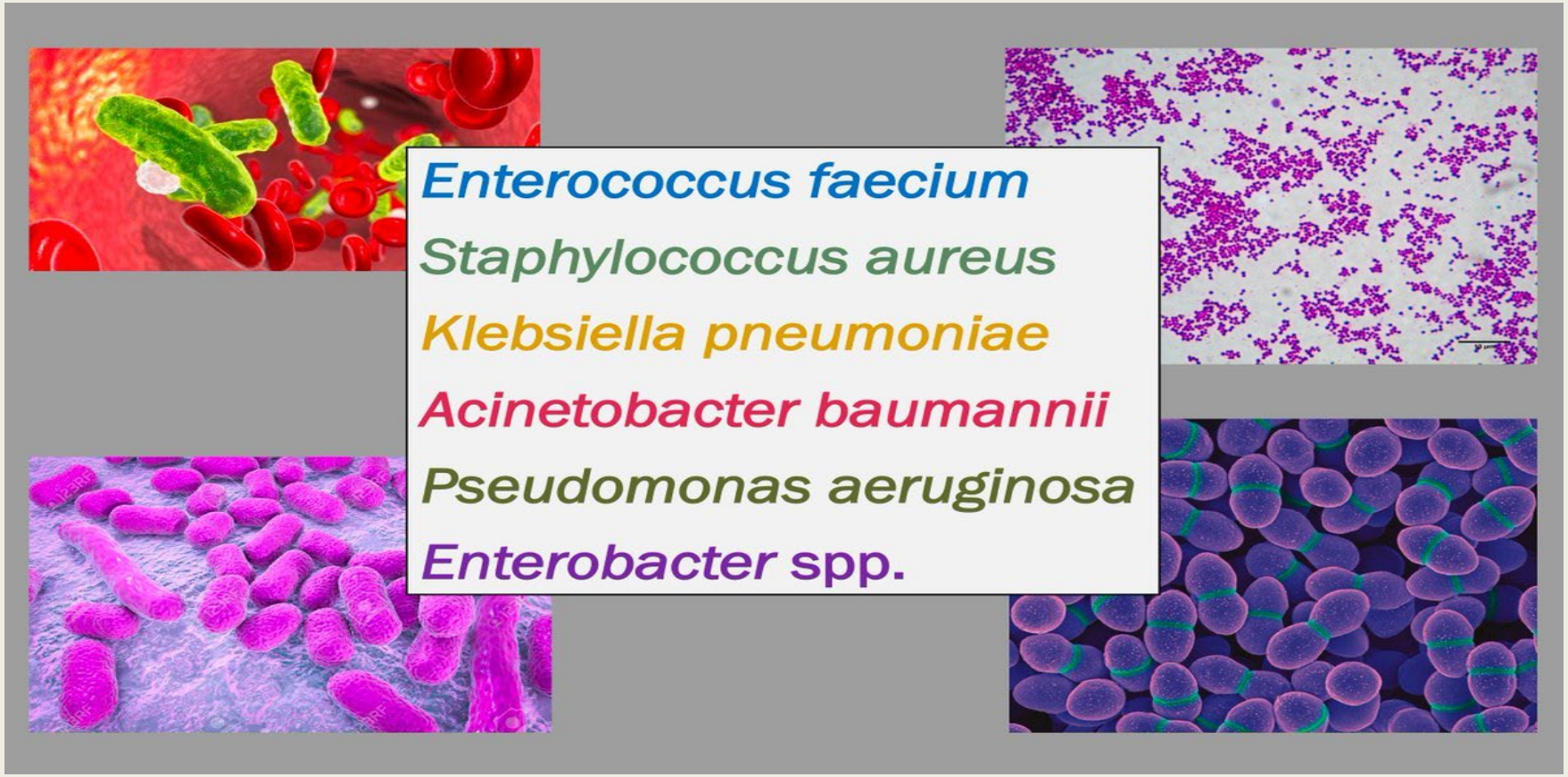
nosocomial acquisition/HAIs

- **Catheter associated urinary tract infection**
  - 40% of all nosocomial infections
- **Ventilator associated pneumonia**
  - 2nd most common
- **Intravascular catheter-related bloodstream infection**

Vincent JL, Rello J, Marshall J, Silva E, Anzueto A, Martin CD, Moreno R, Lipman J, Gomersall C, Sakr Y, Reinhart K, EPIC II Group of Investigators International study of the prevalence and outcomes of infection in intensive care units. JAMA. 2009;302(21):2323

Culprits driving AMR in the ICU

WHO ESKAPE Organisms are all common threats in the ICUs



Epidemiology of AMR in the ICU
The Developing World

- Most studies of **ICU-associated infections** come from industrialized countries
- Rates of infection may be higher in **developing countries**
- Multicenter prospective cohort surveillance study of 46 hospitals in Central and South America, India, Morocco, and Turkey
  - *overall rate of **14.7 % (or 22.5/1000 ICU days)***

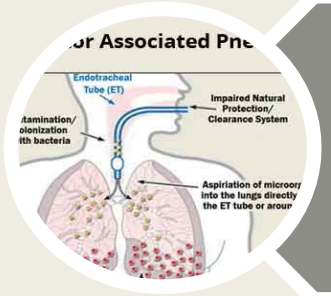
Rosenthal VD, et al. International Nosocomial Infection Control Consortium Members International Nosocomial Infection Control Consortium report, data summary for 2002-2007, issued January 2008. Am J Infect Control. 2008 Nov;36(9):627-37. Epub 2008 Oct 3.

DEVICE SPECIFIC INFECTION RATES

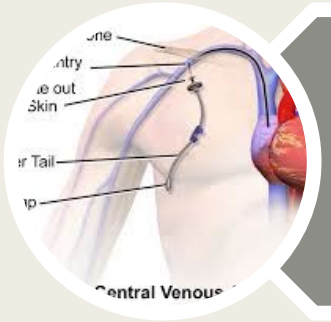
Another study
98 ICUs from Latin America, Asia, Africa, and Europe

1- Device utilization was similar to that reported from ICUs in USA

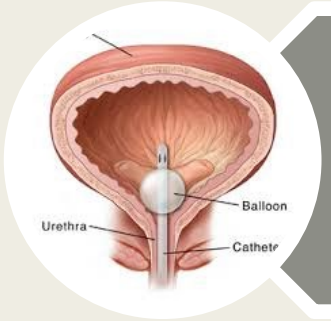
2- Rates of device-associated nosocomial infection were markedly higher in the ICUs from the developing world



VAP 24.1/1000
ventilator days
(range 10.0 to 52.7 cases)



CRBSI 12.5/1000
catheter days
(range 7.8 to 18.5 cases)



CAUTI 8.9/1000
catheter days
(1.7 to 12.8 cases)

Rosenthal VD, et al. International Nosocomial Infection Control Consortium Device-associated nosocomial infections in 55 intensive care units of 8 developing countries. Ann Intern Med. 2006;145(8):582.

Epidemiology of AMR in the ICU in Lebanon

- 70 patients
- **VAP incidence = 47%.**
- **GNR accounted for 83% of all isolates.**
- The most commonly identified organism was **Acinetobacter anitratus**, followed by **Pseudomonas aeruginosa**
- **50% of GNR isolates were classified as antibiotic resistant**
- **Compared with patients without VAP, patients with VAP remained intubated for a longer period and stayed in the intensive care unit longer.**

Kanafani ZA1, Kara L, Hayek S, Kanj SS. Ventilator-associated pneumonia at a tertiary-care center in a developing country: incidence, microbiology, and susceptibility patterns of isolated microorganisms. Infect Control Hosp Epidemiol. 2003 Nov;24(11):864-9.

Epidemiology of AMR in the ICU in Egypt

Ventilator-associated pneumonia (VAP) is the most common hospital-acquired infection among mechanically ventilated patients.

- VAP incidence : **48.8/1000 ventilator days**
- most common GNR was **Klebsiella**
  - *94.6% of isolates resistant to cefotaxime*
  - *70.2% R to imipenem*
  - *100% sensitive to colistin and 94.6% sensitive to tigecycline.*
- most common GP was **Staphylococcus aureus**
  - ***86.6%** of isolates resistant to cefoxitin*
  - *100% were sensitive to teicoplanin, linezolid and tigecycline.*
- The high rates of VAP and the high rates of resistance

  improper implementation of infection control

Azzab MM, El-Sokkary RH, Tawfeek MM, Gebriel MG. Multidrug-resistant bacteria among patients with ventilator associated pneumonia in an emergency intensive care unit, Egypt. East Mediterr Health J. 2017 Feb 1;22(12):894-903.

Epidemiology of AMR in the ICU in Turkey

GNR in ICUs of Istanbul State Hospitals during 2014-2016

Total number of strains isolated: 6000

- Among the non-fermentative bacilli, ***Acinetobacter baumannii*** complex the **most commonly isolated** species
- ***Klebsiella pneumoniae*** most commonly isolated species with maximum antibiotic resistance
  Susceptibility rates for colistin: 73% and 80%.
- ***Escherichia coli*** 2nd most common isolated species among non-urinary bacilli

  had susceptibility rates <90% to carbapenems , colistin and tigecycline.
- Over time: **statistically significant decrease in susceptibility rates against all antibiotics**

Yürüyen C, Daldaban Dinçer Ş, Yanılmaz Ö, Boz ES, Aksaray S.
Surveillance of resistance in the intensive care units using a cumulative antibiogram. Mikrobiyol Bul. 2018 Oct;52(4):329-339. doi: 10.5578/mb.67408.

Epidemiology of AMR in the ICU in Saudi Arabia

A retrospective study was carried out of gram-negative isolates from the adult ICU of King Fahad National Guard Hospital (KFNGH) between 2004 and 2009.

- **Respiratory samples: most indicative of MDROs (63%), followed by urinary samples (57%).**
- Most frequently isolated organisms:
  - ***Acinetobacter baumannii***
  - ***Pseudomonas aeruginosa***
  - ***Escherichia coli***
  - ***Klebsiella pnemoniae***
  - ***Stenotrophomonas maltophilia***
  - ***Enterobacter.***
- ***Antibiotic susceptibility patterns significantly declined***
  - *A baumannii susceptibility to imipenem (55% to 10%), meropenem (33% to 10%), ciprofloxacin (22% to 10%), and amikacin (12% to 6%)*
  - *E coli susceptibility to cefuroxime, ceftazidime, cefotaxime, and cefepime(from 75% to 50% or less)*
  - *S marcescens susceptibility ceftazidime (100% to 35%), and cefepime (100% to 66%)*
  - *Enterobacter susceptibility to ceftazidime (34% to 5%), and pipracillin-tazobactam (51% to 35%)*

Al Johani SM1, Akhter J, Balkhy H, El-Saed A, Younan M, Memish Z. Prevalence of antimicrobial resistance among gram-negative isolates in an adult intensive care unit at a tertiary care center in Saudi Arabia. Ann Saudi Med. 2010 Sep-Oct;30(5):364-9. doi: 10.4103/0256-4947.67073.

Kanafani et al. Antimicrobial Resistance and Infection Control (2018) 7:9
DOI 10.1186/s13756-017-0297-6

Antimicrobial Resistance and Infection Control

RESEARCH Open Access

Multi-drug resistant Acinetobacter species: a seven-year experience from a tertiary care center in Lebanon

Zeina A. Kanafani[1,2†], Nada Zahreddine[2†], Ralph Tayyar[1], Jad Sfeir[1], George F. Araj[3], Ghassan M. Matar[4] and Souha S. Kanj[1,2*]

Abstract

Background: *Acinetobacter* species have become increasingly common in the intensive care units (ICU) over the past two decades, causing serious infections. At the American University of Beirut Medical Center, the incidence of multi-drug resistant *Acinetobacter baumannii* (MDR-Ab) infections in the ICU increased sharply in 2007 by around 120%, and these infections have continued to cause a serious problem to this day.

Methods: We conducted a seven-year prospective cohort study between 2007 and 2014 in the ICU. Early in the epidemic, a case-control study was performed that included MDR-Ab cases diagnosed between 2007 and 2008 and uninfected controls admitted to the ICU during the same time.

Results: The total number of patients with MDR-Ab infections diagnosed between 2007 and 2014 was 128. There were also 99 patients with MDR-Ab colonization without evidence of active infection between 2011 and 2014. The incidence of MDR-Ab transmission was 315.4 cases/1000 ICU patient-days. The majority of infections were considered hospital-acquired (84%) and most consisted of respiratory infections (53.1%). The mortality rate of patients with MDR-Ab ranged from 52% to 66%.

Conclusion: MDR-Ab infections mostly consisted of ventilator-associated pneumonia and were associated with a very high mortality rate. Infection control measures should be reinforced to control the transmission of these organisms in the ICU.

Keywords: Acinetobacter, Intensive care unit, Ventilator-associated pneumonia, Multi-drug resistance, Lebanon

Epidemiology of AMR in the ICU
ACTB MDR

7 year prospective cohort study between 2007 and 2014 in the ICU.

- The total number of patients with MDR-ACTB infections was 128.
- There were also 99 patients with MDR-ACTB colonization without evidence of active infection.
- The incidence of MDR-ACTB transmission was 315.4 cases/1000 ICU patient-days.
- The majority of infections were considered hospital-acquired (84%) and most consisted of respiratory infections (53.1%).
- The mortality rate of patients with MDR-ACTB ranged from 52% to 66%.

Kanafani ZA, Zahreddine N, Tayyar R, Sfeir J, Araj GF, Matar GM, Kanj SS.
Multi-drug resistant Acinetobacter species: a seven-year experience from a tertiary care center in Lebanon. Antimicrob Resist Infect Control. 2018 Jan 22;7:9.

Contributors to the spread of AMR in the ICU

- Older age
- Lack of functional independence and/or decreased cognition
- Presence of underlying comorbid conditions
- Higher severity of acute illness indices
- Long duration of hospitalization prior to the ICU admission (ex. nursing homes)
- Frequent encounters with health care environments (hemodialysis units, IV infusion centers.)

Strich JR, Palmore TN. Preventing Transmission of Multidrug-Resistant Pathogens in the Intensive Care Unit. Infect Dis Clin North Am. 2017 Sep;31(3):535-550. doi: 10.1016/j.idc.2017.05.010. Epub 2017 Jul 5.

Contributors to the spread of AMR in the ICU

Frequent contact with health care personnel concurrently caring for multiple patients

Shared equipment and contaminated environments

- *reservoirs and/or vectors that contribute to acquisition of infections*

Presence of indwelling devices: CVCs, urinary catheters, ETTs

- *bypass natural host defense mechanisms and serve as portals of entry for pathogens*

Recent surgery or other invasive procedures

Receipt of antimicrobial therapy prior to the ICU admission

- *selective pressure promoting the emergence of multidrug-resistant bacteria*

Strich JR, Palmore TN. Preventing Transmission of Multidrug-Resistant Pathogens in the Intensive Care Unit. Infect Dis Clin North Am. 2017 Sep;31(3):535-550. doi: 10.1016/j.idc.2017.05.010. Epub 2017 Jul 5.

Consequences of AMR in the ICU

Infections caused by GN MDROs are associated with:

- **High morbidity and mortality**
- **Significant direct and indirect costs**
- **Prolonged hospitalizations**

due to antibiotic treatment failures

Schwaber MJ, Carmeli Y The effect of antimicrobial resistance on patient outcomes: importance of proper evaluation of appropriate therapy. Crit Care. 2009;13(1):106. Epub 2009 Jan 12
Giske CG, Monnet DL, Cars O, Carmeli Y, ReAct-Action on Antibiotic Resistance Clinical and economic impact of common multidrug-resistant gram-negative bacilli. Antimicrob Agents Chemother. 2008 Mar;52(3):813-21. Epub 2007 Dec 10.

Consequences of antibiotic misuse in the ICU

- **Increasing prevalence of AMR to β-lactam antibiotics**
  - *Pseudomonas aeruginosa*
  - *Acinetobacter baumannii*
  - *Pathogens of the Enterobacteriaceae family*

Treatment options for infections caused by these pathogens are limited.

Time to identification of MDRO delayed

- **Increasing incidence of *C. difficile***

Potential Impact of ASP

TABLE 1] Consequences of Antibiotic Overuse or Misuse and the Potential Impact of an Antibiotic Stewardship Program to Address These Issues

Consequences of Inappropriate Antibiotic Use	Benefits of Antibiotic Stewardship Program
Increased rates of CDI and other nosocomial infections	Decrease in CDI with incidence rate ratio of 0.35[19] Decrease in CDI incidence from 2.2 to 1.4 cases per 1,000 patient-d[20] Decrease in CDI incidence by 60%[21] 52% risk reduction of CDI[22] Decreased rate of CLABSI from 6.9 to 1.2 per 1,000 catheter-d ($P < .05$)[23]
Longer hospital LOS[a]	Mean hospital LOS reduced by 2.9 d[24] Average 3.3-d reduction in length of stay ($P = .0001$)[25]
Increased costs	Antibiotic expenditures decreased by 53%[26] 25% acquisition cost reduction per patient-d[27]
Prolonged treatment durations	Decreased antibiotic use by 55%[28] Decreased duration of treatment from 14.1 to 11.9 d[29] Decreased duration of treatment[30]

CDI = *Clostridium difficile* infection; CLABSI = central line-associated bloodstream infection; LOS = length of stay.
[a]Note that other studies have shown no difference in length of stay with implementation of an antibiotic stewardship program.

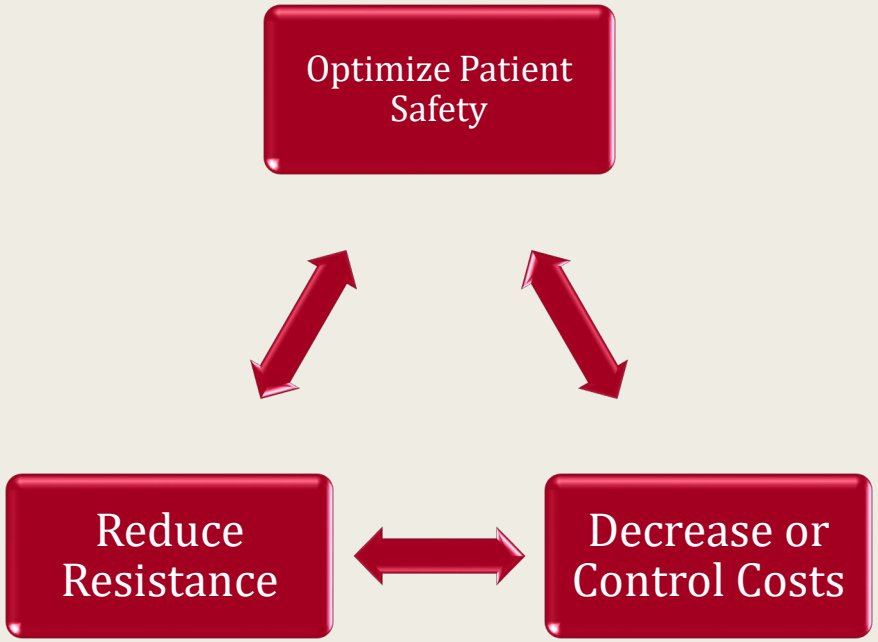
Barriers to successful AMS in the ICU

- **Fear of not adequately covering the causative pathogen/broad spectrum**
  - ***Septic shock***

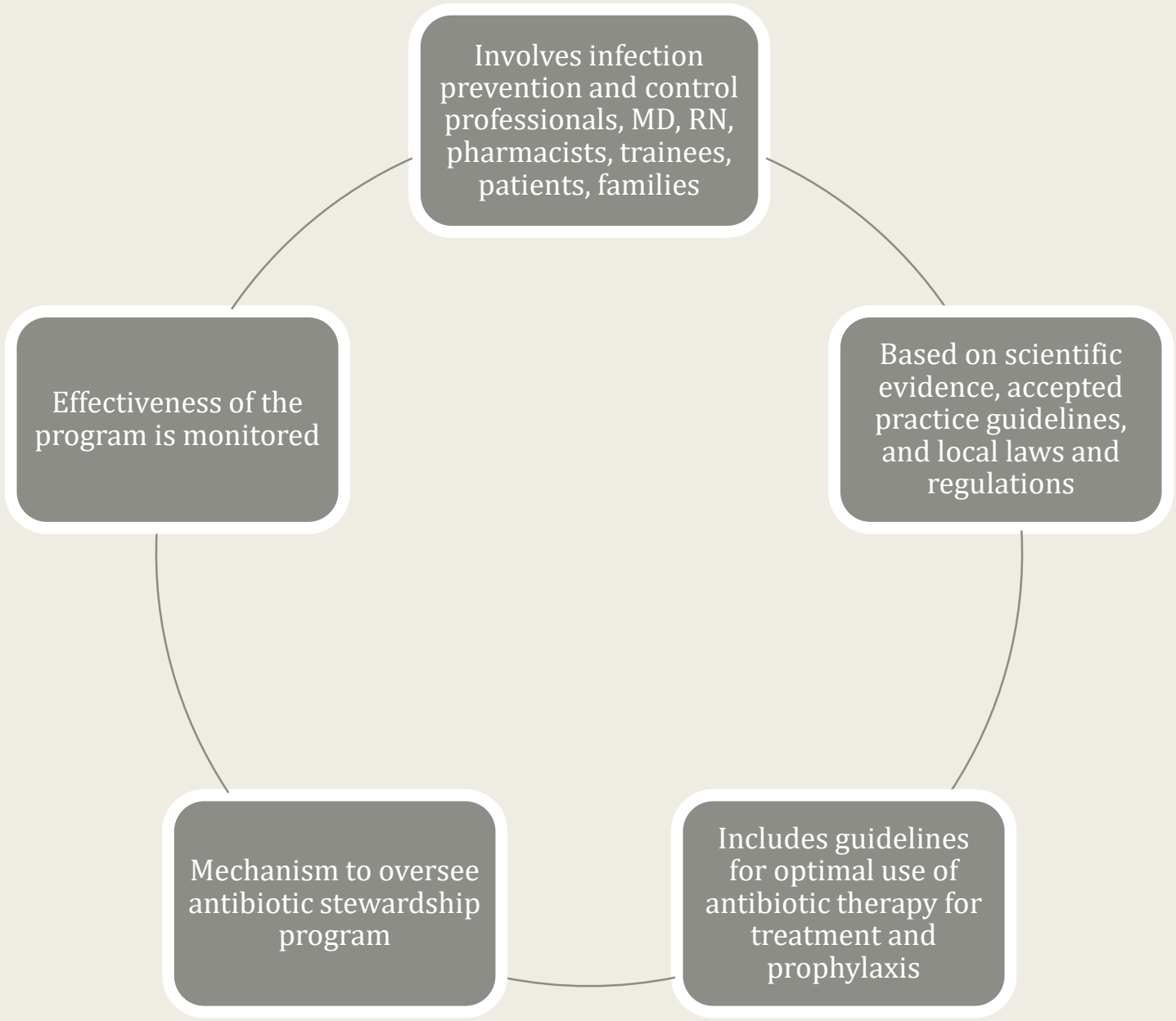
    the time delay associated with increased mortality can be measured in hours
    - patient with septic shock from CAP, no risk factors for MDR pathogens: broad-spectrum combination gram-negative coverage
    - **acute cholecystitis**: community, no recent hospitalization, sepsis: addition of vancomycin
- **Diagnostic uncertainty**
  - ***Pneumonia***
    - **Suspected vs definite diagnosis**
    - **bacterial vs. viral**
    - **Intubated patients: BAL /direct sampling**
      - *European hospital-acquired pneumonia (HAP)/VAP guidelines, the Infectious Diseases Society of America/ American Thoracic Society (IDSA/ATS) guidelines*
  - ***Urinary tract infections***
    - **Colonization vs. real infection**
- **Underappreciation of the toxicity of antibiotics**

Pickens, Chiagozie I. et al. Principles and Practice of Antibiotic Stewardship in the ICU. CHEST, Volume 156, Issue 1, 163 – 171.
Campion M, Scully G. Antibiotic Use in the Intensive Care Unit: Optimization and De-Escalation. J Intensive Care Med. 2018 Dec;33(12):647-655.
De Waele et al. Antimicrobial resistance and antibiotic stewardship programs in the ICU: insistence and persistence in the fight against resistance. A position statement from ESICM/ESCMID/WAAAR round table on multi-drug resistance. Intensive Care Med. 2018 Feb;44(2):189-196.

ROLE of the ASP



Goal: provide patients requiring antibiotic treatment with the right antibiotics, at the right time, at the right dose, and for the right duration



ASHP 2016, Pharmacist Guide to Antimicrobial Stewardship

ANTIMICROBIAL STEWARDSHIP PROGRAM

•Multidisciplinary team approach

Prospective Audits/Interventions

- Include the following types: de-escalation, IV to PO switch, duration of therapy, duplicate therapy
- Quantitative and qualitative measures
- Report compliance rate of interventions

Retrospective Audits/Reviews

- Days of therapy for carbapenem class
- Defined daily doses all antimicrobials
- Targeted reports on classes of antibiotics and review of medication use evaluations

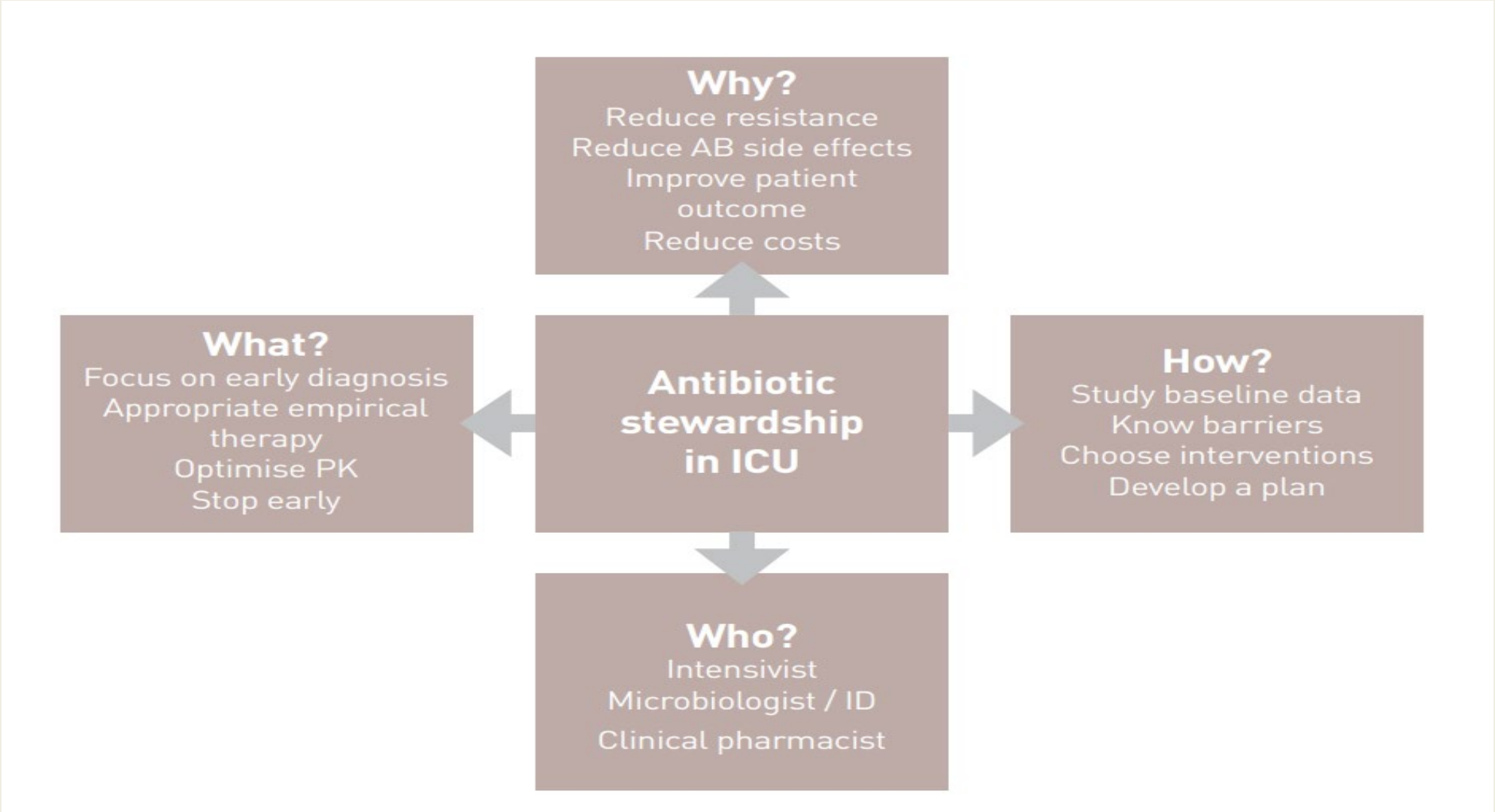
ASP Rounds/Educational Sessions

- Therapeutic monitoring of antibiotics ➔Audience: medical residents (core curriculum), pharmacists, ID fellows
- Introduction to antimicrobial stewardship ➔ Audience: ID fellows
- Updates in antimicrobial stewardship ➔Audience: ID division, pharmacists

Order Sets

- Febrile Neutropenia
- Perioperative antibiotics
- Continuous/extended infusion of beta-lactams in the critical care areas
- Antibiotic lock therapy

Key elements of AMS in the ICU



https://healthmanagement.org/uploads/article_attachment/icu-v17-schouten-antimicrobial.pdf

Key elements of AMS in the ICU

Leadership

The role of hospital leadership is primordial

but…

great benefit from

- **integration** of ASP with ICU leadership
- **building collaborative practice** and **sharing of antibiotic utilization** data between the ASP and ICU leadership

Key elements of AMS in the ICU

The Role of Bundles

	Antibiotic Care Bundle for ICU Patients
T0	• Documentation of rationale for antibiotic initiation
	• Collection of appropriate culture specimen
	• Appropriate empirical selection of antibiotics
+48-72hrs	• De-escalation /stopping antibiotics based on evidence
	• Selection of appropriate agents for definitive therapy
	• IV to PO switch when possible
	• Monitor antibiotic drug levels

Cooke, F. J.; Holmes, A. H. The missing care bundle: antibiotic prescribing in hospitals. Int. J. Antimicrob. Agents, 2007, 30 (1), 25-29.
Pulcini, C.; Defres, S.; Aggarwal, I.; Nathwani, D.; Davey, P. Design of a 'day 3 bundle' to improve the reassessment of inpatient empirical antibiotic prescriptions. J. Antimicrob. Chemother., 2008, 61(6), 1384-1388.
Toth, N. R.; Chambers, R. M.; Davis, S. L. Implementation of a care bundle for antimicrobial stewardship. Am. J. Health Syst. Pharm., 2010, 67 (9), 746-749.

Key elements of AMS in the ICU

Prospective Audit and Feedback

Several studies to assess the acceptance rate and antibiotic use

Re-evaluation of the choice of antibiotics based on diagnostic results

Contact the provider with alternative recommendations if antimicrobial use is considered to be unjustified on the basis of predetermined criteria.

390 of 1,429 (27.3%) study-ABX courses were assessed as unjustified

recommendations to modify or stop therapy were accepted for 260 (66.7%) of these courses

Antibiotic use decreased significantly during the intervention period

Onorato L et al. The effect of an antimicrobial stewardship programme in two intensive care units of a teaching hospital: an interrupted time series analysis. Clin Microbiol Infect. 2019 Oct 31. pii: S1198-743X(19)30557-9.

Cosgrove, S., Seo, S., Bolon, M., Sepkowitz, K., Climo, M., Diekema, D., . . . Perl, T. (2012). Evaluation of Postprescription Review and Feedback as a Method of Promoting Rational Antimicrobial Use: A Multicenter Intervention. Infection Control & Hospital Epidemiology, 33(4), 374-380.

Handshake Stewardship

- New, specific ASP model
- Involves prospective review of hospital-wide **antimicrobial** ordering
- Includes a compressed “second look” of relevant clinical and historical patient data

- **In-person recommendations are then provided directly to the medical team.**

Key elements of AMS in the ICU

The role of the Microbiologist

microbiologist consultant should attend daily ICU rounds

Table 1 Overview of areas of expertise and involvement of the clinical microbiologist in the ICU

Core domains of the clinical microbiologist in ICU	Frequency	Activities (other than daily rounds)
Assisting physicians in diagnosis and empirical treatment	Daily	On-call availability, rapid results communication and consultation, guidelines development
Aiding in interpretation of results	Daily	Report with note for contamination/colonization, selective reporting on antimicrobial susceptibilities, educational meeting
Avoiding unnecessary testing	Daily	Educational campaigns, audit and feedback, electronic ordering implementation
Assisting in correct microbiological sampling techniques and timing thereof	Daily	On-call availability, guidelines development, educational meetings on new and advanced diagnostic tests
Assisting in selecting the optimal targeted antibiotic and the correct duration	From daily to weekly	Periodical meetings, on-call availability, selective reporting of antibiotic susceptibilities, computer-decision support system, guidelines development
Providing cumulative surveillance data on resistant organisms for infection control purposes	From every 3 months or 6 months to 1 year	Hospital intranet, printed card, educational meeting
Facilitating infection prevention and control practices	Daily	On-call availability, guidelines development, educational meetings

Schouten, J., De Angelis, G. & De Waele, J.J. A microbiologist consultant should attend daily ICU rounds. Intensive Care Med (2019).

Key elements of AMS in the ICU
The Role of the EMR

- **Antibiotic Time-Outs**
  - *encourage clinicians to take ownership of the antibiotic review process*
  - *require less direct ASP involvement*
    - Time-outs led to antimicrobial duration being defined 63% of the time and deescalation or discontinuation of antimicrobials 29% of the time.
    - Total acquisition cost was 31 % lower for piperacillin/tazobactam and vancomycin and 46% for meropenem
- **Clinical Pathways and Clinical Decision Support**
  - *Integrated in the EMR to offer alternative antibiotics*
  - *Alerts for inappaoriate use based on microbiological data*
  - *Alerts for toxicities*
  - *DDIs*

Adams SM, Ngo L, Morphew T, Babbitt CJ. Does an Antimicrobial Time-Out Impact the Duration of Therapy of Antimicrobials in the PICU? Pediatr Crit Care Med. 2019 Jun;20(6):560-567.
Burston J, Adhikari S, Hayen A, Doolan H, Kelly ML, Fu K, Jensen TO, Konecny P. A Role for Antimicrobial Stewardship in Clinical Sepsis Pathways: a Prospective Interventional Study. Infect Control Hosp Epidemiol. 2017 Sep;38(9):1032-1038.

PROCESS MEASURES OF THE ASP - AUBMC

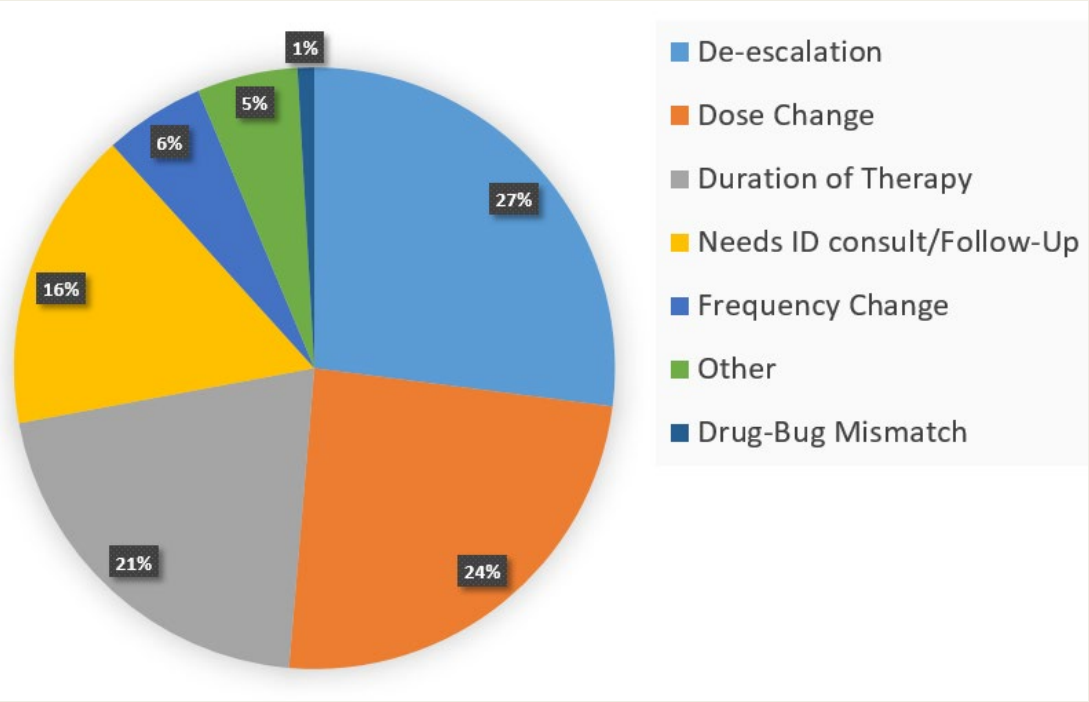
Prospective Process Measures

- Appropriate duration of therapy
- Appropriate antibiotic drug choice post 48-72h of therapy initiation
- Rate of acceptance of antimicrobial stewardship recommendations
- Appropriateness of antibiotic drug regimen

Retrospective Process Measures

- **Defined Daily Dose (DDD) for antimicrobials**
- **Duration of Therapy (DOT) for carbapenems**
- Restricted antimicrobial usage rate in percentage
- Rate of adherence to guidelines, care bundles, policies
- Appropriateness of time of initiation of pre-operative antibiotic
- Appropriateness of time of initiation of therapy with respect to cultures
- Impact Assessment (C diff rates, MDROs…)
- Antibiotic cost per patient-day

ASSESSING APPROPRIATENESS OF THERAPY

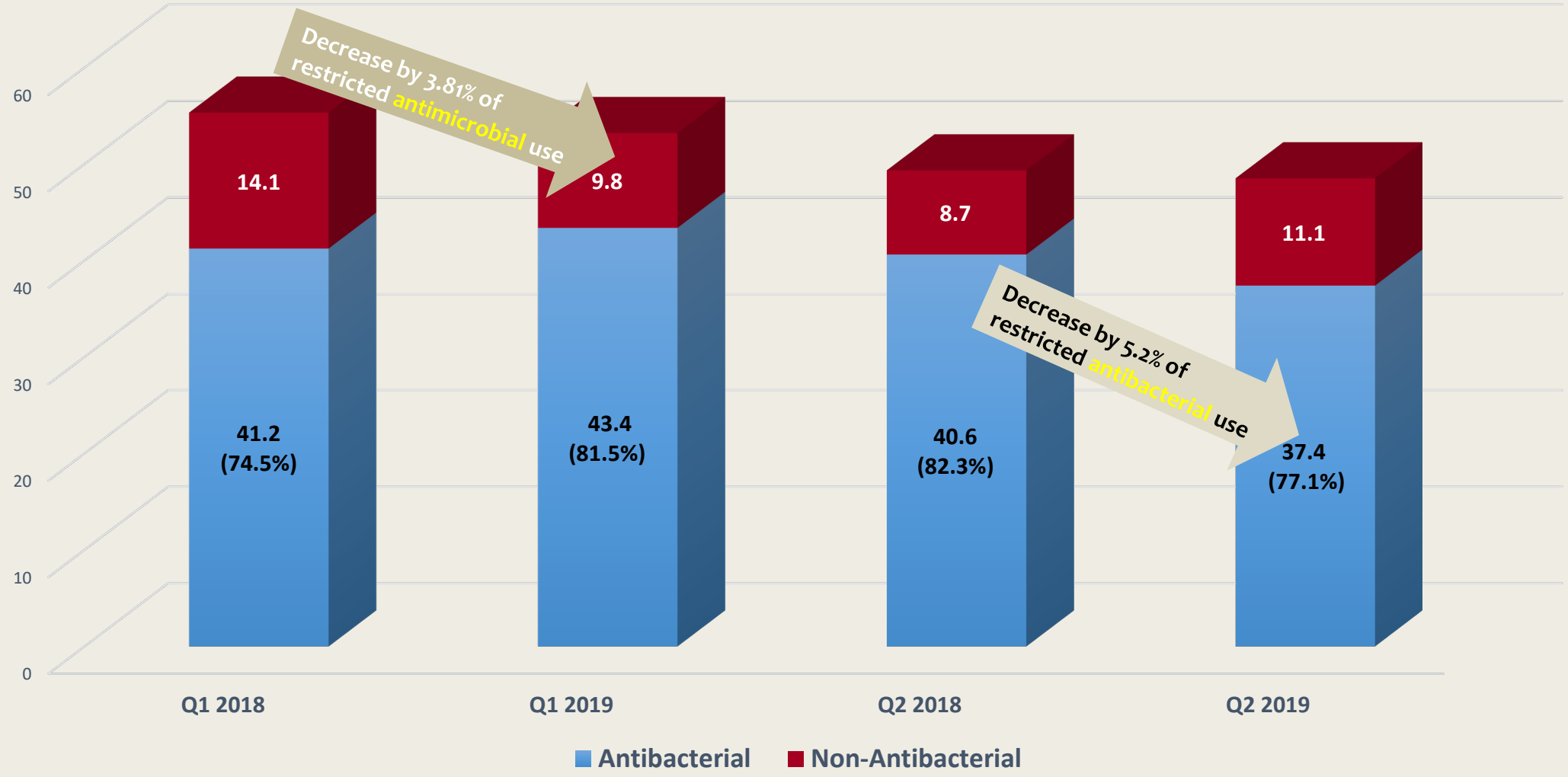


ASSESSED PARAMETER	APPROPRIATE (%)	NOT APPROPRIATE (%)
INDICATION	157 (87%)	24 (13%)
DURATION	156 (86%)	25 (14%)
DOSE	147 (81%)	34 (19%)

48% of interventions resulted in reduction of carbapenem usage

ASP IMPACT

Defined Daily Dose – Restricted Antimicrobials



original article

Antimicrobial stewardship program implementation in a medical intensive care unit at a tertiary care hospital in Saudi Arabia

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Correspondence: Dr. Abdulrazaq S. Al-Jazairi - Head, Medical/Critical Pharmacy Department, Division of Pharmacy Services, King Faisal Specialist Hospital and Research Centre, PO Box 3354, MBC-11, Riyadh 11211, Saudi Arabia - T: +966-11-4427603 F: +966-11-4427608 - ajazairi@kfshrc.edu.sa

Ann Saudi Med 2013; 33(6): 547-554

DOI: 10.5144/0256-4947.2013.547

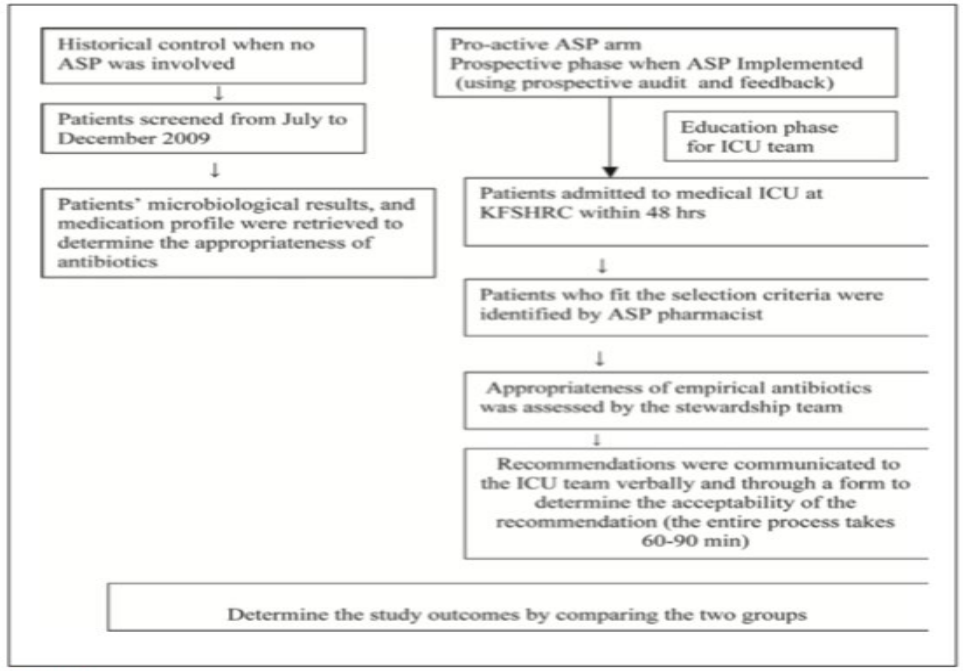


Figure 1. Study design showing historical control phase (in left side) and prospective phase of ASP (in right side). ASP: Antimicrobial Stewardship Program; ICU: Intensive Care Unit; KFSHRC: King Faisal Specialist Hospital & Research Center

Table 1. ASP strategies and current status at KFSHRC.

	Strategy	Advantages	Disadvantages	Current status at KFSHRC
Proactive Core Strategies	Formulary restriction and preapproval strategies (A-I /A-II)	Cost savings Encourage use of antibiotics in hospital formulary	Loss of autonomy	Active: restrict the use by certain prescribers, disease state, or units
	Prospective audit and feedback (A-I)	Direct interaction with prescriber Post hoc education and remediation Retains autonomy	Resource-intensive unless computerized feedback	Under consideration in this study
Supplemental Strategies	Education (A-III and B-II)	Informational, may increase knowledge Prescriber remains independent	Passive education not effective	Active: grand rounds, journal club, departmental conferences, e-mail alerts
	Guidelines (A-I)	Standardize practice and decreases variance	Loss of independence	Active: evidence-based guideline developed by AUE subcommittee based on local resistance patterns, national guidelines
	Antimicrobial order forms (B-II)	Use of information technology to display guidelines, make suggestions	Resource-intensive	Case-by-case basis using CPOE-based system and EMR
	Pharmacodynamic dose optimization (AII)	Optimal use of currently available antimicrobials based on organism, site of infection, and patient characteristics	Education of nursing staff might require for appropriate time to withdraw blood level	Active: on-call schedule is designed to contribute the clinical pharmacists and pharmacy residents competence in patient care
	Antimicrobial cycling (C-II)	Scheduled rotation of antimicrobials in specific sequenceà may reduce resistance by selective pressure	Loss of autonomy Theoretical concerns about effectiveness	Case-by-case basis

A-I: Good evidence with properly randomized controlled trials (RCT).

A-II: Good evidence from randomized controlled trials (RCT), cohort, or case-controlled.

A-III: Moderate evidence to support a recommendation for use from RCT.

B-II: Moderate evidence to support a recommendation from RCT, cohort, or case-controlled.

C-II: Poor evidence to support a recommendation based on clinical experience, descriptive studies, or reports of expert committees.

ASP: Antimicrobial stewardship program, AUE: antimicrobial utilization and evaluation, CPOE: computerized physician order entry, EMR: electronic medical record, KFSHRC: King Faisal Specialist Hospital & Research Center.

Amer MR, Akhras NS, Mahmood WA, Al-Jazairi AS.
Antimicrobial stewardship program implementation in a medical intensive care unit at a tertiary care hospital in Saudi Arabia. Ann Saudi Med. 2013 Nov-Dec;33(6):547-54.

Table 4. Results: Empirical antibiotics therapy appropriateness.

	Control (N=49)	Active ASP (N=24)	*P* value
Initial appropriateness			
Appropriate, no. (%)- change	15 (30.6%)	5 (20.8%)	.379
Final appropriateness			
Appropriate, no. (%)-change	15 (30.6%)	24 (100%)	.0001
Reasons for initial antibiotics inappropriateness[a]			
No current treatment for positive culture	9	0	.02
No indication (e.g., colonization) for current treatment	5	0	.15
Inadequate empiric coverage for indication	14	10	.37
Excessive empiric coverage for indication	2	2	.6
Resistant to current antibiotic	12	1	.02
Regimen excessive (failure to de-escalate)	8	0	.04
Regimen inadequate (wrong dose or frequency)	6	10	.006
Total	56	23	

ASP: Antimicrobial stewardship program.

[a]Each patient with initial inappropriate AB ≥ 1 reason for inappropriateness.

Control and Elimination of Extensively Drug-Resistant Acinetobacter baumanii in an ICU in Lebanon

Figure 1

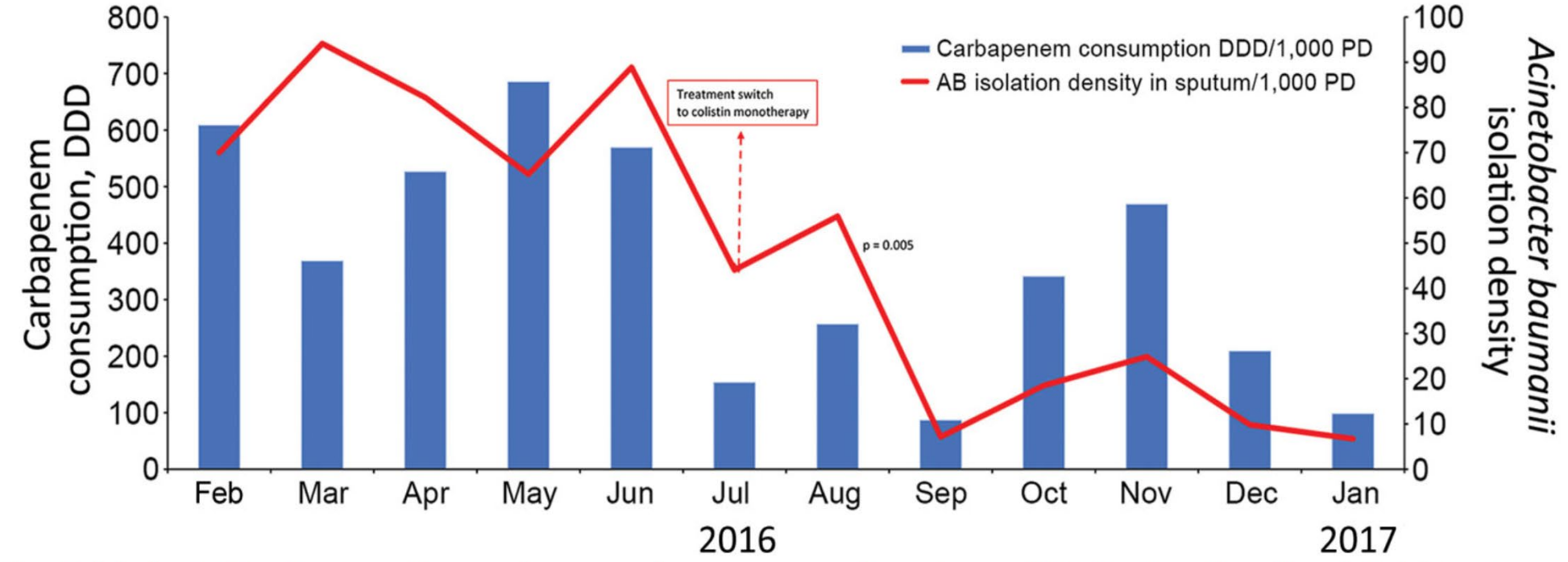


Figure 1. Isolation density of *Acinetobacter baumanii* in sputum cultures versus carbapenem consumption in the intensive care unit (ICU) of Saint Georges Hospital University Medical Center, Beirut, Lebanon, during February 1, 2016–January 31, 2017. Rates are measured per 1,000 patient-days. Dashed arrow represents the beginning of period 2 in which we implemented a carbapenem-sparing regimen. DDD, defined daily dose; PD, patient days.

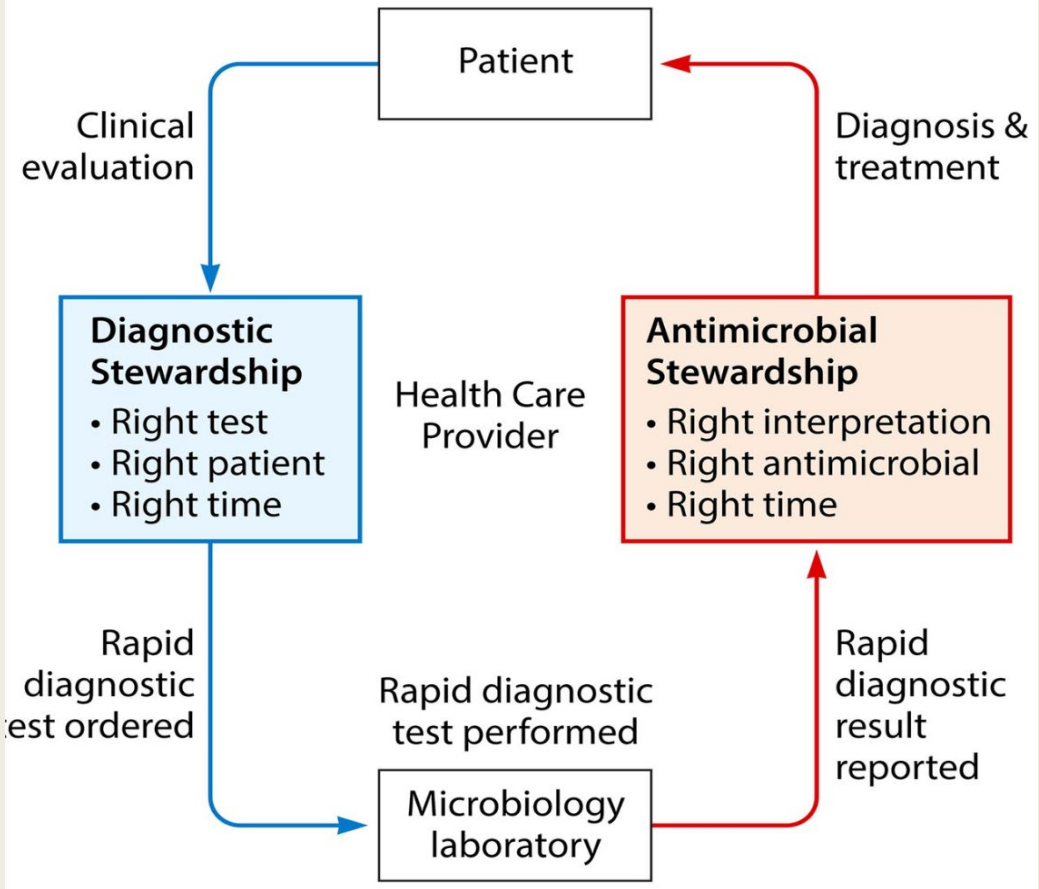
Chamieh A, Nawfal T, Ballouz T, Afif C, Juvelekian G, Hlais S, et al. Control and Elimination of Extensively Drug-Resistant Acinetobacter baumanii in an Intensive Care Unit. Emerg Infect Dis. 2019;25(10):1928-1931.

ROLE OF NOVEL DIAGNOSTICS

Rapid Diagnostic and Laboratory Testing to Reduce Inappropriate Antibiotics

And shorten the duration to effective therapy

- rapid molecular diagnostic tests more readily available
- may address the greatest barrier to antibiotic stewardship in the ICU: diagnosis
- PCR panels for rapid detection of respiratory viruses are commonly used
- Data for rapid diagnostic testing for bacterial and fungal infections in the ICU are more limited.



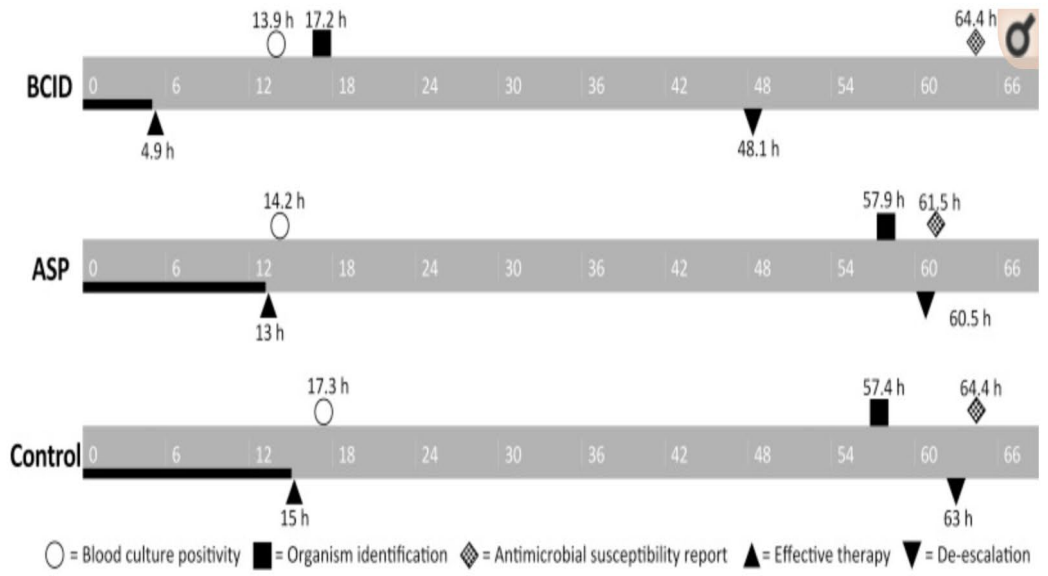
Kevin Messacar, Sarah K. Parker, James K. Todd, Samuel R. Dominguez
Implementation of Rapid Molecular Infectious Disease Diagnostics: the Role of Diagnostic and Antimicrobial StewardshipJournal of Clinical Microbiology Feb 2017, 55 (3) 715-723

AMERICAN SOCIETY FOR MICROBIOLOGY | Journal of Clinical Microbiology

Benefits of Adding a Rapid PCR-Based Blood Culture Identification Panel to an Established Antimicrobial Stewardship Program

Shawn H. MacVane,[a,b] Frederick S. Nolte[c]
Department of Pharmacy,[a] Division of Infectious Diseases,[b] and Department of Pathology and Laboratory Medicine,[c] Medical University of South Carolina, Charleston, South Carolina, USA

- In patients with BSI, ASP alone improved antimicrobial utilization
- **Addition** of BCID to an established ASP **shortened the time to effective therapy** and further improved antimicrobial use compared to ASP alone



Timeline for microbiology and antimicrobial therapy among study groups. Symbols represent the median values for the study population. Abbreviations: ASP, antimicrobial stewardship program; BCID, blood culture identification panel.

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journal homepage: www.elsevier.com/locate/ijid

The Impact of Integrating Rapid PCR-Based Blood Culture Identification Panel to an Established Antimicrobial Stewardship Program in the United Arab of Emirates

Rama Nasef[a,*], Rania El Lababidi[a], Adnan Alatoom[b], Sumathi Krishnaprasad[c], Fernanda Bonilla[d]

[a] Department of Pharmacy, Cleveland Clinic Abu Dhabi, Abu Dhabi, United Arab Emirates
[b] Cleveland Clinic Laboratory, Cleveland Clinic Abu Dhabi, Abu Dhabi, United Arab Emirates
[c] Department of Business Intelligence and Statistical Analysis, Cleveland Clinic Abu Dhabi, Abu Dhabi, United Arab Emirates
[d] Department of Infectious Disease, Cleveland Clinic Abu Dhabi, Abu Dhabi, United Arab Emirates

hospitalized patients with BSI

positive blood cultures on BCID were studied in 2 groups:

- *conventional culture with ASP (AS)*
- *BCID with ASP (BCID).*

The primary outcomes were time to first appropriate antimicrobial therapy, infection related length of stay (LOS), ICU admission, 14 days bacteremia recurrence and in-hospital mortality. Secondary outcomes were 30 days reinfection rate, hospital cost and ASP interventions.

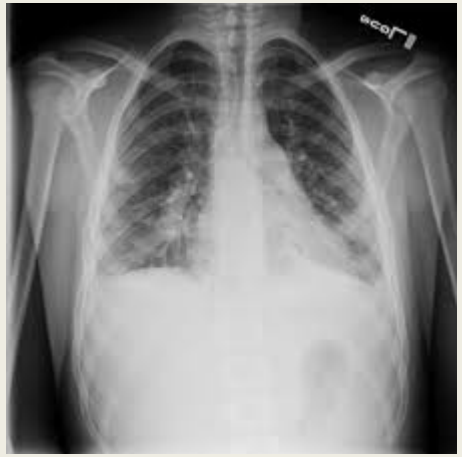
Results

- Out of total 477 positive blood cultures, 206 (AS and BCID) with real BSI were included.
- The time needed for organism identification was shorter in the BCID group than in the AS group (1.3 h vs. 51 h; P = 0.0002).
- BCID had a shorter time to appropriate antimicrobial therapy than AS (17.8 h vs.45 h; P = 0.0004).
- No statistical difference was observed in mortality rate, 14 days bacteremia recurrence, ICU admission, hospital cost, LOS or ASP interventions.

Nasal Methicillin-Resistant *Staphylococcus aureus* (MRSA) PCR Testing Reduces the Duration of MRSA-Targeted Therapy in Patients with Suspected MRSA Pneumonia

And reduce unnecessary therapy

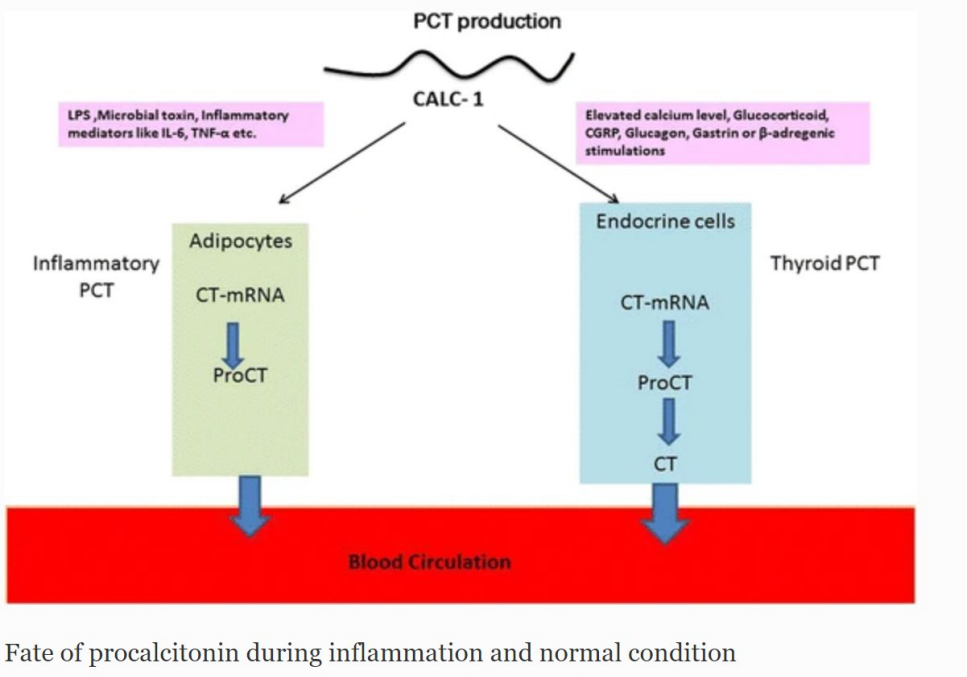
- MRSA-associated pneumonia rate 2.0% to 2.5% over a 5-year period
- In a multicentered observational study, *S. aureus* was isolated in 37 of 2,259 (1.6%) patients and was more common in winter months (coinciding with influenza season), critically ill patients, and older patients.



- the use of nasal MRSA PCR testing reduced the duration of vancomycin and linezolid by approximately **2 days** without any deleterious effects to patients' clinical courses.

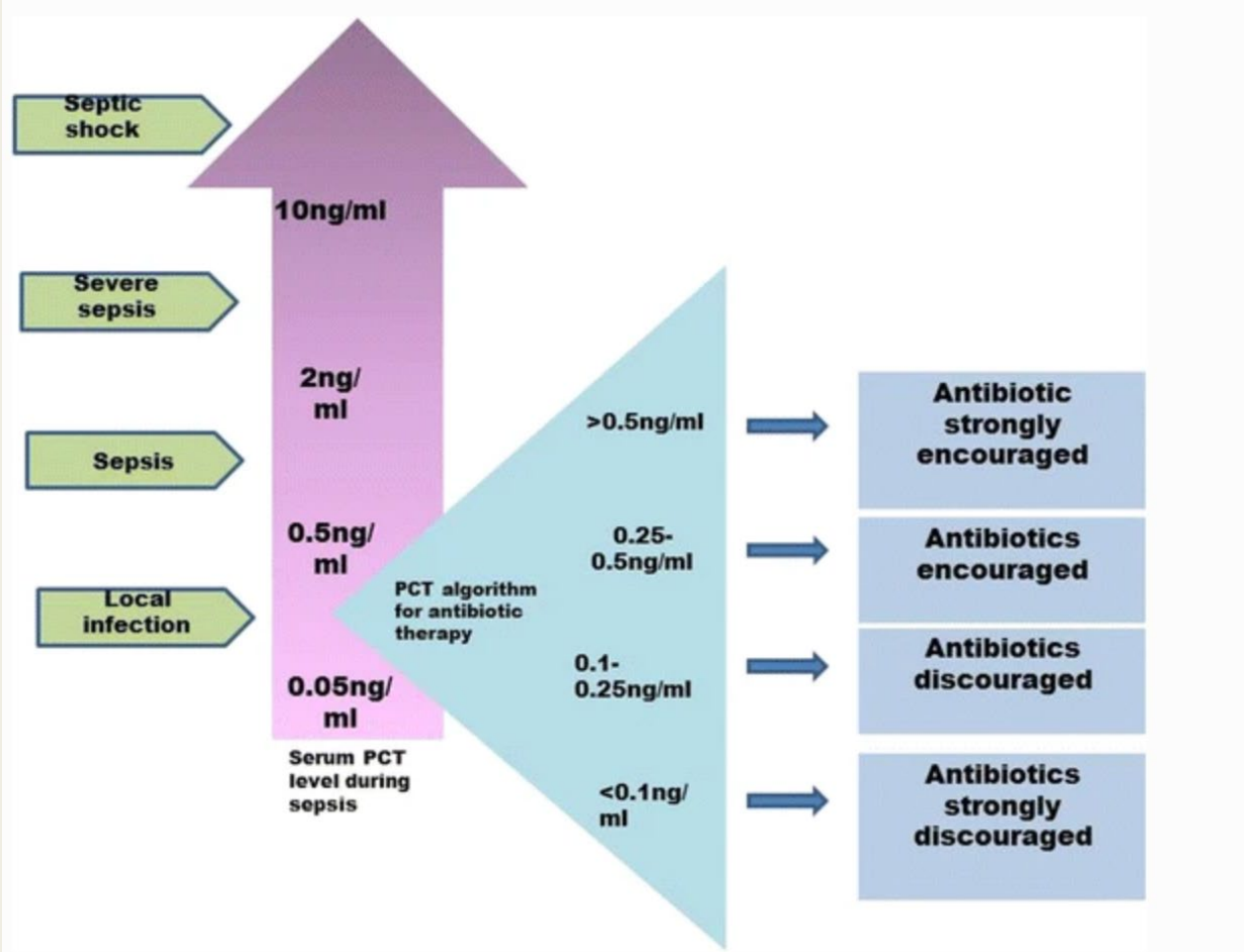
Baby N, Faust AC, Smith T, Sheperd LA, Knoll L, Goodman EL. Nasal Methicillin-Resistant Staphylococcus aureus (MRSA) PCR Testing Reduces the Duration of MRSA-Targeted Therapy in Patients with Suspected MRSA Pneumonia. Antimicrob Agents Chemother. 2017;61(4):e02432-16. Published 2017 Mar 24.

ROLE OF PROCALCITONIN



Fate of procalcitonin during inflammation and normal condition

During inflammation, PCT is produced mainly by two alternative mechanisms; direct pathway induced by lipopolysaccharide (LPS) or other toxic metabolite from microbes and indirect pathway induced by various inflammatory mediators like IL-6, TNF-α, etc.



PCT algorithm for antibiotic therapy

Role of Procalcitonin in the Management of CAP and shock

- Elevated PCT levels do not discriminate between the major categories of shock
  - ***normal PCT eliminates a bacterial etiology of the shock in 95% of patients.***
- In patients with CAP + PCT level 0.25 ng/mL
  - *likelihood of invasive bacterial etiology is 5%*
  - *differentiate between invasive disease and colonization*
- For both severe CAP and bacteremic septic shock:
  - ***sequential PCT levels assist in both assessing source control and determining the duration of antimicrobial therapy.***

Gilbert DN. Role of Procalcitonin in the Management of Infected Patients in the Intensive Care Unit. Infect Dis Clin North Am. 2017 Sep;31(3):435-453.

Role of Procalcitonin in the ICU

META ANALYSIS

- Procalcitonin-guided antibiotic treatment in ICU patients with infection and sepsis:
  - ***in improved survival***
  - ***lower antibiotic treatment duration***

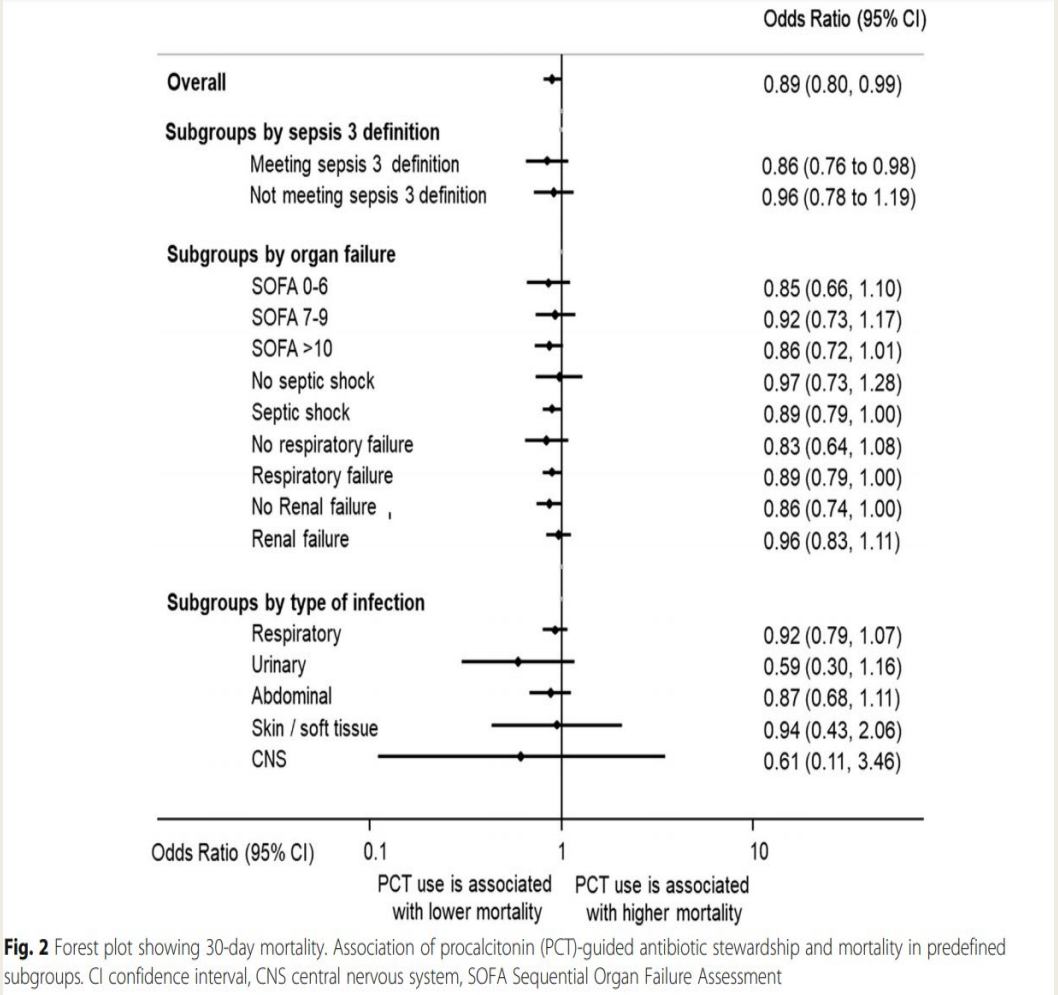


Fig. 2 Forest plot showing 30-day mortality. Association of procalcitonin (PCT)-guided antibiotic stewardship and mortality in predefined subgroups. CI confidence interval, CNS central nervous system, SOFA Sequential Organ Failure Assessment

Wirz, Y., Meier, M.A., Bouadma, L. et al. Effect of procalcitonin-guided antibiotic treatment on clinical outcomes in intensive care unit patients with infection and sepsis patients: a patient-level meta-analysis of randomized trials. Crit Care 22, 191 (2018).

ROLE OF PROCALCITONIN

- **PROS:**
  - *Studies in severely ill patients have found a survival advantage to the shorter duration of antibiotics when guided by PCT levels.*
  - *Serial procalcitonin (PCT) values may be used to shorten antibiotic duration for patients with severe sepsis and septic shock.*
  - *Serial specimen more helpful than a single assay*
- **CONS:**
  - *PCT is less likely to have a benefit when shorter courses are the standard: HAP/VAP*
  - *Empirical escalation of therapy in patients with rising PCT has been associated with adverse outcomes*
  - *Optimal management of patients with a persistent inflammatory state is unclear*

Strich JR, Palmore TN. Preventing Transmission of Multidrug-Resistant Pathogens in the Intensive Care Unit. Infect Dis Clin North Am. 2017 Sep;31(3):535-550.

Role of Infection Control

Infection control is the cornerstone on which antibiotic stewardship programs are built.

Prevention of infection results in decreased antibiotic use and decreases antibiotic resistance pressure.

Hand hygiene, antimicrobial stewardship, and reduction in device use remain the low-technology interventions that could have a major impact on nosocomial transmission of antimicrobial-resistant organisms.

Role of Infection Control
Hand hygiene

Standard strategies include mandatory hand hygiene for all health-care workers:

- **bacterial colonization is present on the majority of HCWs hands**
- **2/3 of ICU HCWs carry Candida species on their hands**

With the use of hand hygiene, transmission of bacteria from employee to patient is reduced.

Hand cleansing with alcohol-based solutions is most effective and provides the longest time periods of compliance.

De Waele JJ. Antimicrobial resistance and antibiotic stewardship programs in the ICU: insistence and persistence in the fight against resistance. A position statement from ESICM/ESCMID/WAAAR round table on multi-drug resistance. Intensive Care Med. 2018 Feb;44(2):189-196.

Role of Infection Control
Active Surveillance

- Local epidemiologic data
- Point prevalence testing
- Surveillance testing
- Outbreak investigations

De Waele JJ. Antimicrobial resistance and antibiotic stewardship programs in the ICU: insistence and persistence in the fight against resistance. A position statement from ESICM/ESCMID/WAAAR round table on multi-drug resistance. Intensive Care Med. 2018 Feb;44(2):189-196.

Optimizing antibiotic usage

- Extended Infusion of beta lactams
- Carbapenem sparing strategies
- Shorter duration of therapy

Campion M, Scully G.
Antibiotic Use in the Intensive Care Unit: Optimization and De-Escalation. J Intensive Care Med. 2018 Dec;33(12):647-655. doi: 10.1177/0885066618762747. Epub 2018 Mar 13.

Extended infusion of beta-lactam antibiotics: optimizing therapy in critically-ill patients in the era of antimicrobial resistance

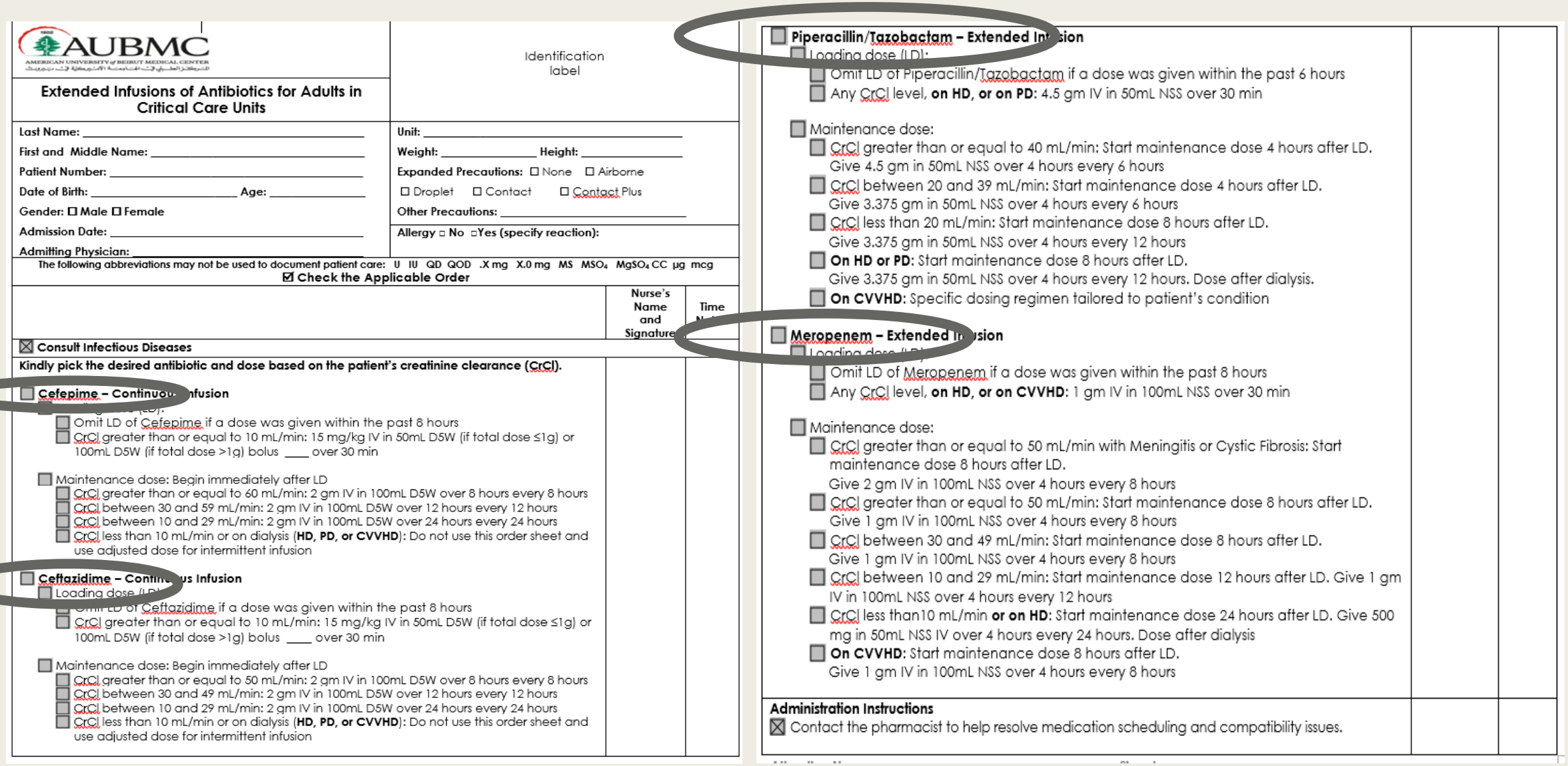
Nesrine A. Rizk*, Zeina A. Kanafani*, Hussam Z. Tabaja and Souha S. Kanj

Division of Infectious Diseases, Department of Internal Medicine, American University of Beirut Medical Center, Beirut, Lebanon

- Prolonged infusion is an alternative dosing approach that promises to provide higher fT > MIC necessary for the bactericidal effect of beta-lactam agents.
- Clinical trials are generally supportive of this concept, although some have failed to demonstrate an improved clinical outcome with prolonged infusion.
- EI/CI is favored in the ICU where the PK/PD of antibiotics are altered and the MICs against isolated pathogens are higher.

Expert Rev Anti Infect Ther. 2017 Jul;15(7):645-652. doi: 10.1080/14787210.2017.1348894. Epub 2017 Jul 3.
Extended infusion of beta-lactam antibiotics: optimizing therapy in critically-ill patients in the era of antimicrobial resistance.
Rizk NA1, Kanafani ZA1, Tabaja HZ1, Kanj SS1.

Extended Infusion Order Set in the ICU



AUBMC
AMERICAN UNIVERSITY of BEIRUT MEDICAL CENTER

Extended Infusions of Antibiotics for Adults in Critical Care Units

Identification label

Last Name: _____
First and Middle Name: _____
Patient Number: _____
Date of Birth: _____ Age: _____
Gender: ☐ Male ☐ Female
Admission Date: _____
Admitting Physician: _____

Unit: _____
Weight: _____ Height: _____
Expanded Precautions: ☐ None ☐ Airborne
☐ Droplet ☐ Contact ☐ Contact Plus
Other Precautions: _____
Allergy ☐ No ☐ Yes (specify reaction):

The following abbreviations may not be used to document patient care: U IU QD QOD .X mg X.0 mg MS MSO_4 $MgSO_4$ CC µg mcg

☑ Check the Applicable Order

Nurse's Name and Signature | Time

☒ **Consult Infectious Diseases**

Kindly pick the desired antibiotic and dose based on the patient's creatinine clearance (CrCl).

☐ **Cefepime – Continuous Infusion**
☐ Loading dose (LD):
☐ Omit LD of Cefepime if a dose was given within the past 8 hours
☐ CrCl greater than or equal to 10 mL/min: 15 mg/kg IV in 50mL D5W (if total dose ≤1g) or 100mL D5W (if total dose >1g) bolus ____ over 30 min

☐ Maintenance dose: Begin immediately after LD
☐ CrCl greater than or equal to 60 mL/min: 2 gm IV in 100mL D5W over 8 hours every 8 hours
☐ CrCl between 30 and 59 mL/min: 2 gm IV in 100mL D5W over 12 hours every 12 hours
☐ CrCl between 10 and 29 mL/min: 2 gm IV in 100mL D5W over 24 hours every 24 hours
☐ CrCl less than 10 mL/min or on dialysis (**HD, PD, or CVVHD**): Do not use this order sheet and use adjusted dose for intermittent infusion

☐ **Ceftazidime – Continuous Infusion**
☐ Loading dose (LD):
☐ Omit LD of Ceftazidime if a dose was given within the past 8 hours
☐ CrCl greater than or equal to 10 mL/min: 15 mg/kg IV in 50mL D5W (if total dose ≤1g) or 100mL D5W (if total dose >1g) bolus ____ over 30 min

☐ Maintenance dose: Begin immediately after LD
☐ CrCl greater than or equal to 50 mL/min: 2 gm IV in 100mL D5W over 8 hours every 8 hours
☐ CrCl between 30 and 49 mL/min: 2 gm IV in 100mL D5W over 12 hours every 12 hours
☐ CrCl between 10 and 29 mL/min: 2 gm IV in 100mL D5W over 24 hours every 24 hours
☐ CrCl less than 10 mL/min or on dialysis (**HD, PD, or CVVHD**): Do not use this order sheet and use adjusted dose for intermittent infusion

☐ **Piperacillin/Tazobactam – Extended Infusion**
☐ Loading dose (LD):
☐ Omit LD of Piperacillin/Tazobactam if a dose was given within the past 6 hours
☐ Any CrCl level, **on HD, or on PD:** 4.5 gm IV in 50mL NSS over 30 min

☐ Maintenance dose:
☐ CrCl greater than or equal to 40 mL/min: Start maintenance dose 4 hours after LD. Give 4.5 gm in 50mL NSS over 4 hours every 6 hours
☐ CrCl between 20 and 39 mL/min: Start maintenance dose 4 hours after LD. Give 3.375 gm in 50mL NSS over 4 hours every 6 hours
☐ CrCl less than 20 mL/min: Start maintenance dose 8 hours after LD. Give 3.375 gm in 50mL NSS over 4 hours every 12 hours
☐ **On HD or PD:** Start maintenance dose 8 hours after LD. Give 3.375 gm in 50mL NSS over 4 hours every 12 hours. Dose after dialysis.
☐ **On CVVHD:** Specific dosing regimen tailored to patient's condition

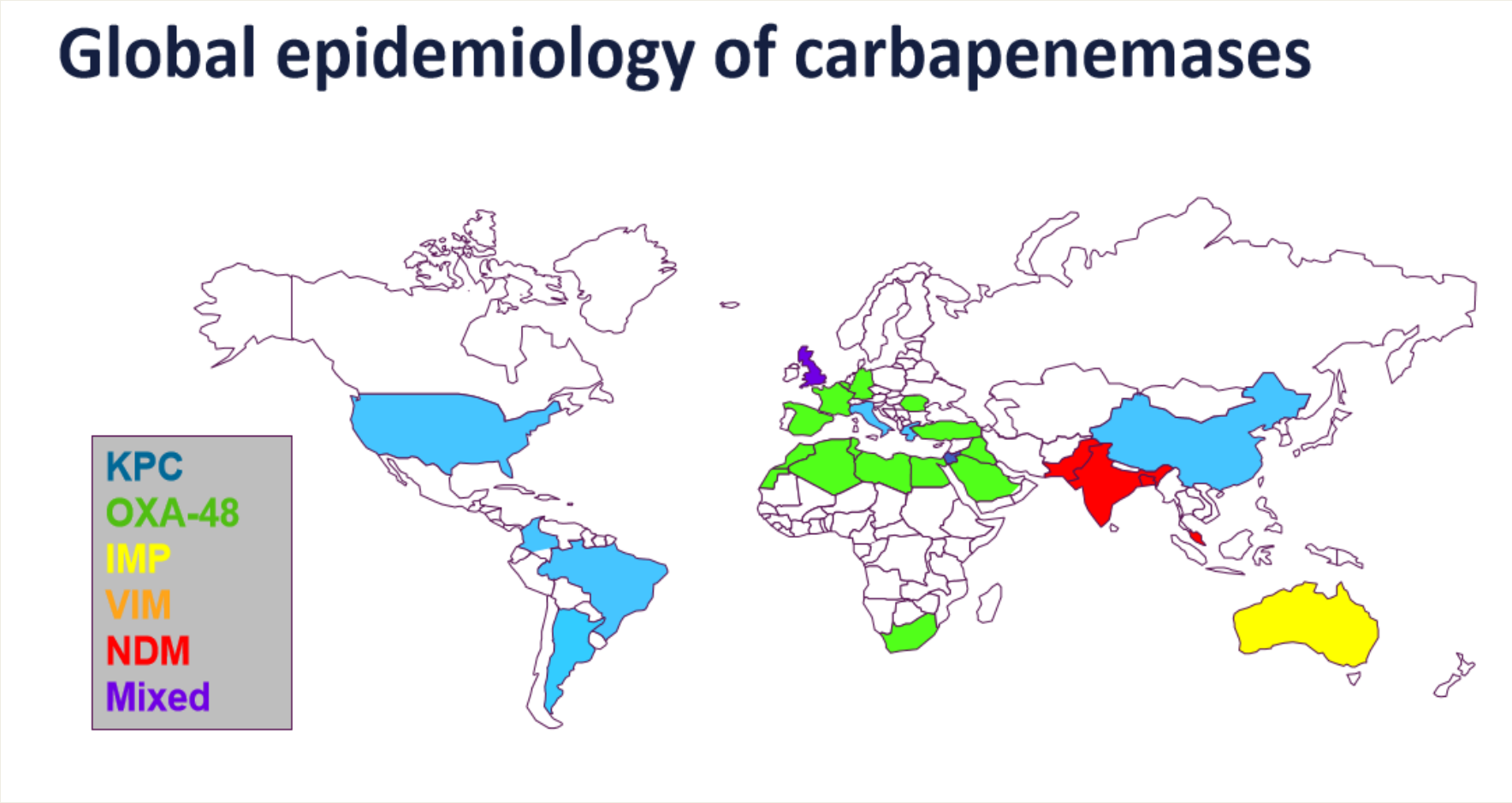
☐ **Meropenem – Extended Infusion**
☐ Loading dose (LD):
☐ Omit LD of Meropenem if a dose was given within the past 8 hours
☐ Any CrCl level, **on HD, or on CVVHD:** 1 gm IV in 100mL NSS over 30 min

☐ Maintenance dose:
☐ CrCl greater than or equal to 50 mL/min with Meningitis or Cystic Fibrosis: Start maintenance dose 8 hours after LD. Give 2 gm IV in 100mL NSS over 4 hours every 8 hours
☐ CrCl greater than or equal to 50 mL/min: Start maintenance dose 8 hours after LD. Give 1 gm IV in 100mL NSS over 4 hours every 8 hours
☐ CrCl between 30 and 49 mL/min: Start maintenance dose 8 hours after LD. Give 1 gm IV in 100mL NSS over 4 hours every 8 hours
☐ CrCl between 10 and 29 mL/min: Start maintenance dose 12 hours after LD. Give 1 gm IV in 100mL NSS over 4 hours every 12 hours
☐ CrCl less than10 mL/min **or on HD:** Start maintenance dose 24 hours after LD. Give 500 mg in 50mL NSS IV over 4 hours every 24 hours. Dose after dialysis
☐ **On CVVHD:** Start maintenance dose 8 hours after LD. Give 1 gm IV in 100mL NSS over 4 hours every 8 hours

Administration Instructions
☒ Contact the pharmacist to help resolve medication scheduling and compatibility issues.

GLOBAL CARBAPENEM RESISTANCE

- Alarming rates of carbapenem resistance
- **WHO:** list of antibiotic-resistant "priority pathogens"
  - Multi-drug resistant organisms including Acinetobacter and carbapenem-resistant Enterobacteriaceae
- Association between carbapenem use and emerging resistance



NOVEL ANTIBIOTIC COMBINATIONS

Antimicrobial Therapies - Coverage

Antibiotics	ESBL	CRE	MDR PSA	CRA
Ceftolozane-Tazobactam				
Ceftazidime-Avibactam		OXA-48, KPC		
Meropenem-Vaborbactam		KPC		
Imipenem-Relebactam		KPC		
Plazomicin				
Eravacycline				
Cefiderocol				

PROSPECTIVE AUDITS

Carbapenem Restriction

Used the electronic medical record and all **Interventions** were recorded and followed

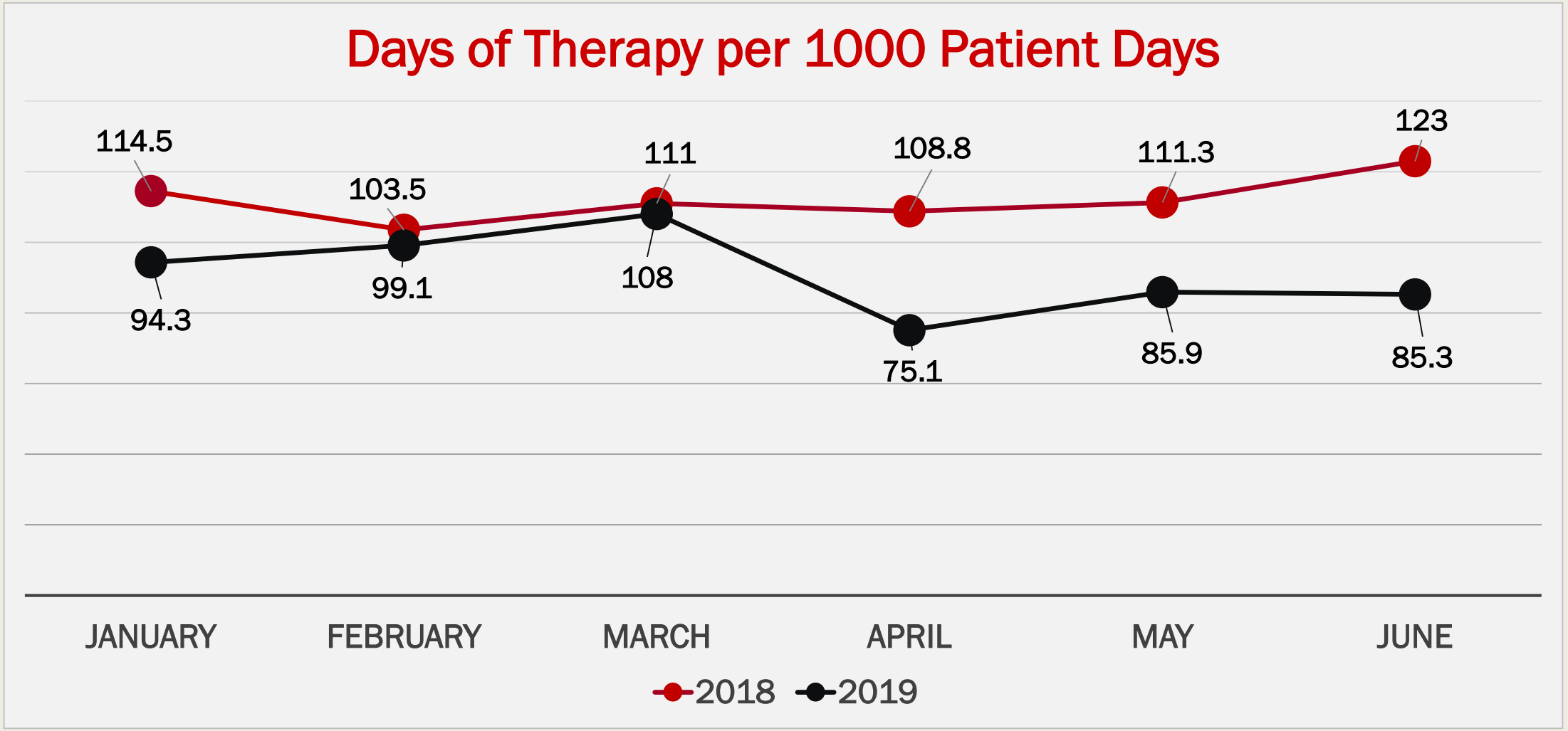
Population screened

Major findings reported

- Quantification and classification of antimicrobial stewardship interventions
- Assessing appropriateness of therapy
  - Indication: empiric versus targeted therapy
  - Dose
  - Duration

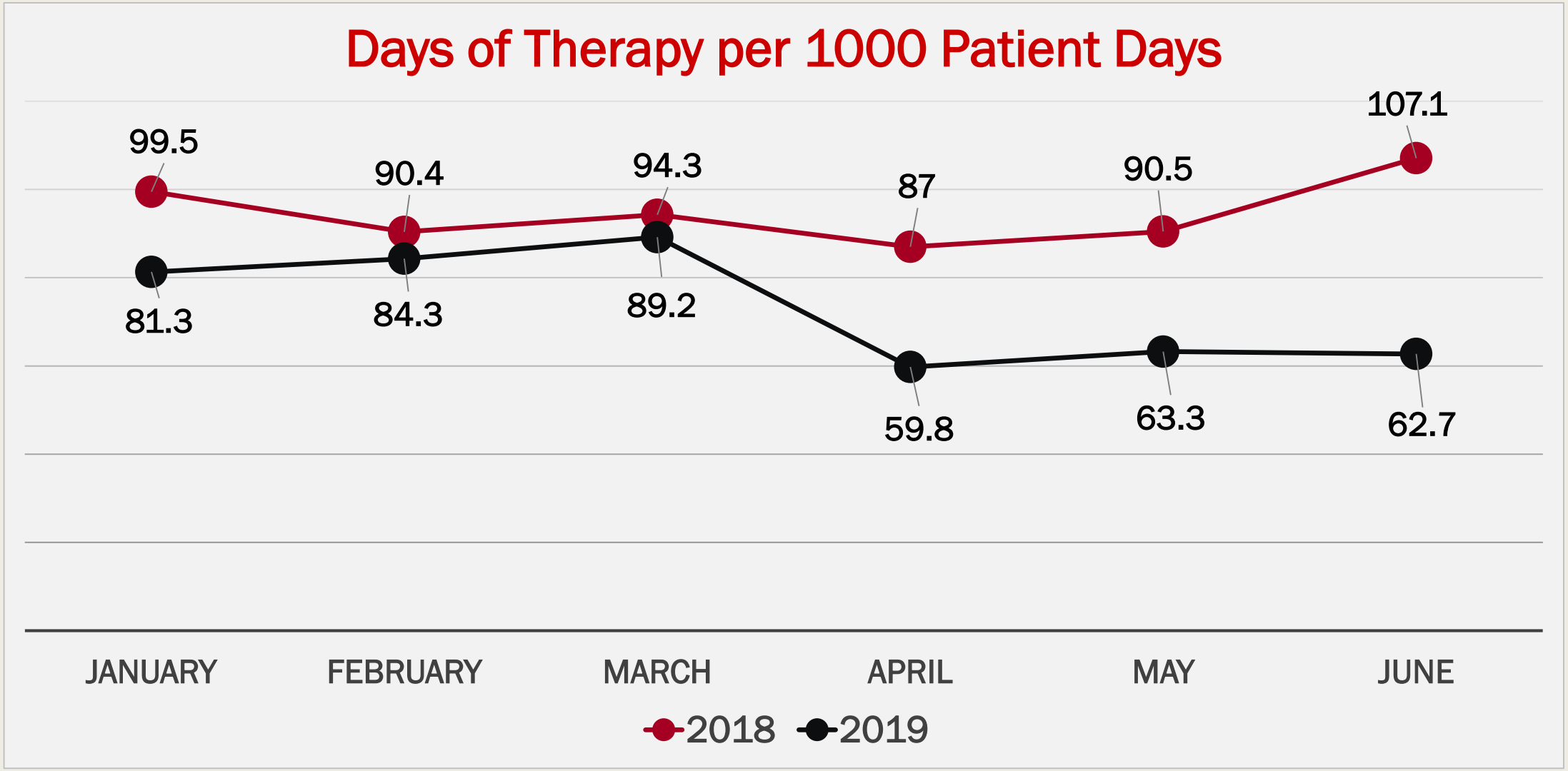
ASP IMPACT

Days of Therapy – All Carbapenems



ASP IMPACT

Days of Therapy – Carbapenems with Anti-Pseudomonal Coverage



Actively Reduce Antibiotic Treatment Duration in ICU

Actively Reduce Antibiotic Treatment Duration in ICU

Applicability of The Short Duration of BSI

Courtesy of Dr Souha Kanj

Included	Excluded

• Stable at day 7
• Mildly ill (SOFA score 2)
• Infection sources
  • Urinary
  • Abdominal
• Types of bacteria
  • Enterobacteriaceae
  • E. Coli
  • Klebsiella
	• Unstable patients
	• Critically ill
	• **Infection sources**
	  • Lack of source control
	  • Endocarditis
	• **Types of bacteria**
	  • Non-fermenters
	  • Pseudomonas
	  • Acinetobacter

Yahav D *et al. Clin Infect Dis* 2019;7:1091

SHORTER IS BETTER
LESS IS MORE

Courtesy of Dr Nisrine Haddad

Short-Course Therapy for Common Infections

Infection	Short Course (days)	Long Course (days)
Acute Bacterial Skin and Skin Structure Infection	5-6	10
Acute Exacerbation of Chronic Bronchitis/COPD	≤ 5	≥ 7
Community Acquired Pneumonia	3 or 5	7, 8, or 10
Cystitis	3 (FQ)	3 (BL)
Complicated Urinary Tract Infections/Pyelonephritis	5 or 7	10 or 14
Febrile Neutropenia	Afebrile & stable x 72h	Afebrile & stable x 72h, ANC > 500
Gram Negative Bloodstream Infection	7	14
Hospital Acquired/Ventilator Associated Pneumonia	7-8	14-15
Intraabdominal Infections	4 or 8	10 or 15
Osteomyelitis	42	84

Thank you


MEDICATION
education
resistance
safety
Antimicrobial
RESPONSIBILITY
ANTIMICROBIAL
ANTIMICROBIAL STEWARDSHIP
antibiotics
responsibility
SAFETY
medication
Stewardship
judicious
stewardship
STEWARDSHIP
JUDICIOUS
antimicrobial
ORGANISMS