Early Diagnostics and Appropriate Antibiotic Selection in Critically Ill Patient

Faran Ahmad, MBBS FACP
Assistant Professor, ID & Critical Care Medicine
Creighton University

- I have no disclosures
- No off-label medication discussed

Objectives

- Highlight the importance and strategies for early diagnostics of infectious etiologies in critically ill patient
- Discuss the strategies to improve clinical decision making regarding antimicrobial dosing
- Understand the criteria for appropriate antibiotic selection

Early Diagnosis of Infections in Critical Illness

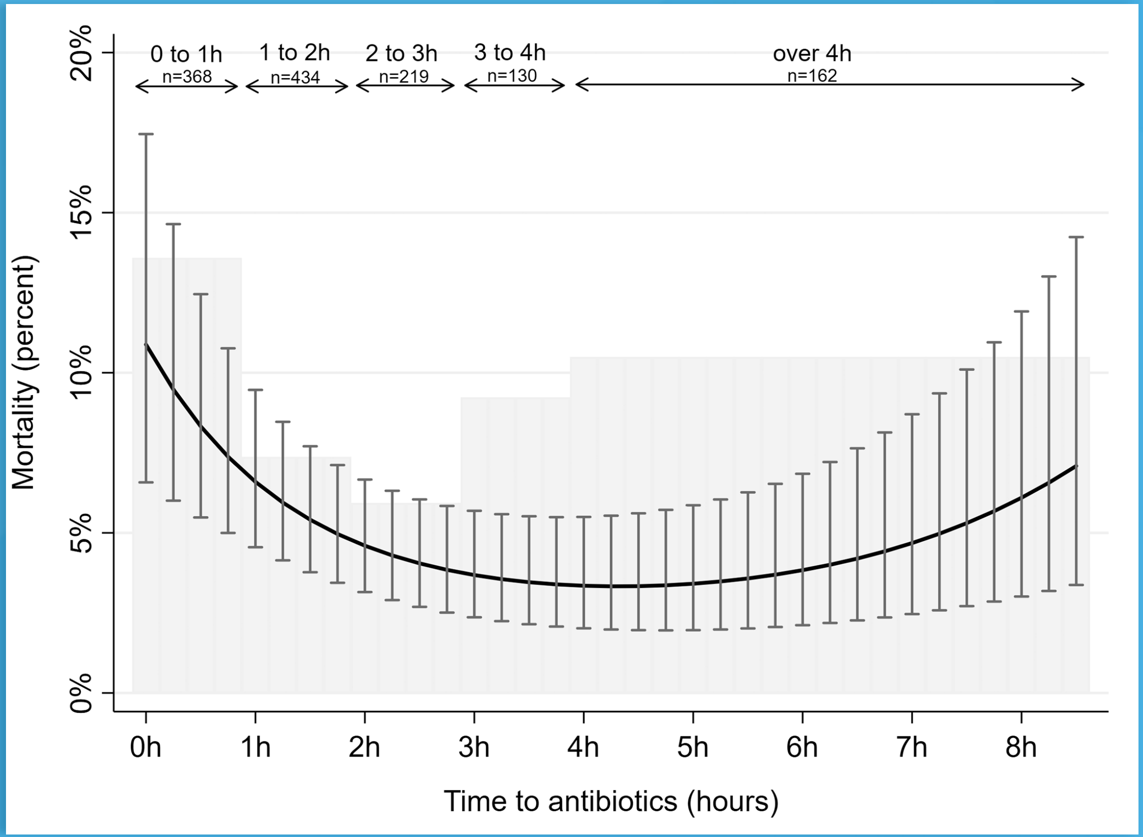
Why detection of infection in critically ill patients is complex ?

- Patients are unable to communicate due to pain, agitation, encephalopathy, and/or intubation
- Typical signs of infection may be masked due to ongoing interventions
- Negative diagnostic workup is only valid for limited amount of time
- Atypical & opportunistic pathogens
- Fear of “missing” an infection leading to broad spectrum antibiotics

Creighton UNIVERSITY

Early Diagnosis of Infections in Critical Illness

- Observational study from 24 emergency departments in Norway - 1559 patients with infection and at least two SIRS criteria
- Timeline of diagnostic procedures for recognizing sepsis in emergency departments
- Did not include severity of illness or source control attempt



Model-predicted 30-day all-cause mortality according to time to antibiotic treatment in minutes, adjusted for patient's age, date of admission and presence of organ failure

Creighton University

PLoS One. 2020;15(1):e0227652

DIRECT Approach to Early Diagnosis

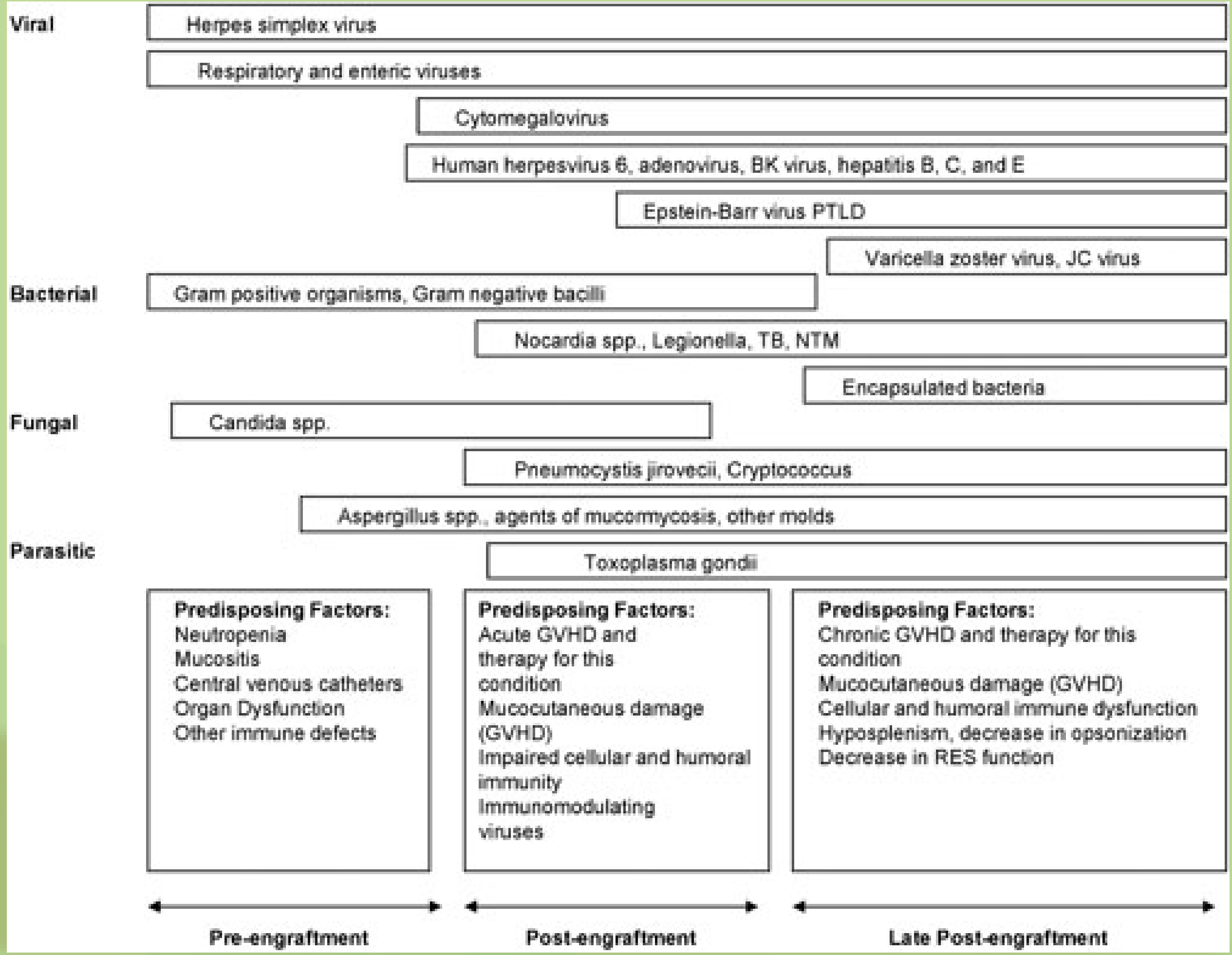
D	Delay: Time since respiratory symptoms onset, since antibiotic prophylaxis or treatment, since transplantation
I	Immune deficiency: nature of immune defects and ongoing antibiotic prophylaxis
R	Radiographic appearance: Consolidation, air bronchogram, nodules, interstitial pattern, pleural effusion, mediastinal mass, cardiomegaly, pericarditis
E	Experience: the clinical experience of the ICU team and consultants
CT	Better description of the radiographic patterns

Intensive Care Med 46, 298–314 (2020)

Creighton University

DIRECT Approach to Early Diagnosis

Delay:
Time since immune suppression



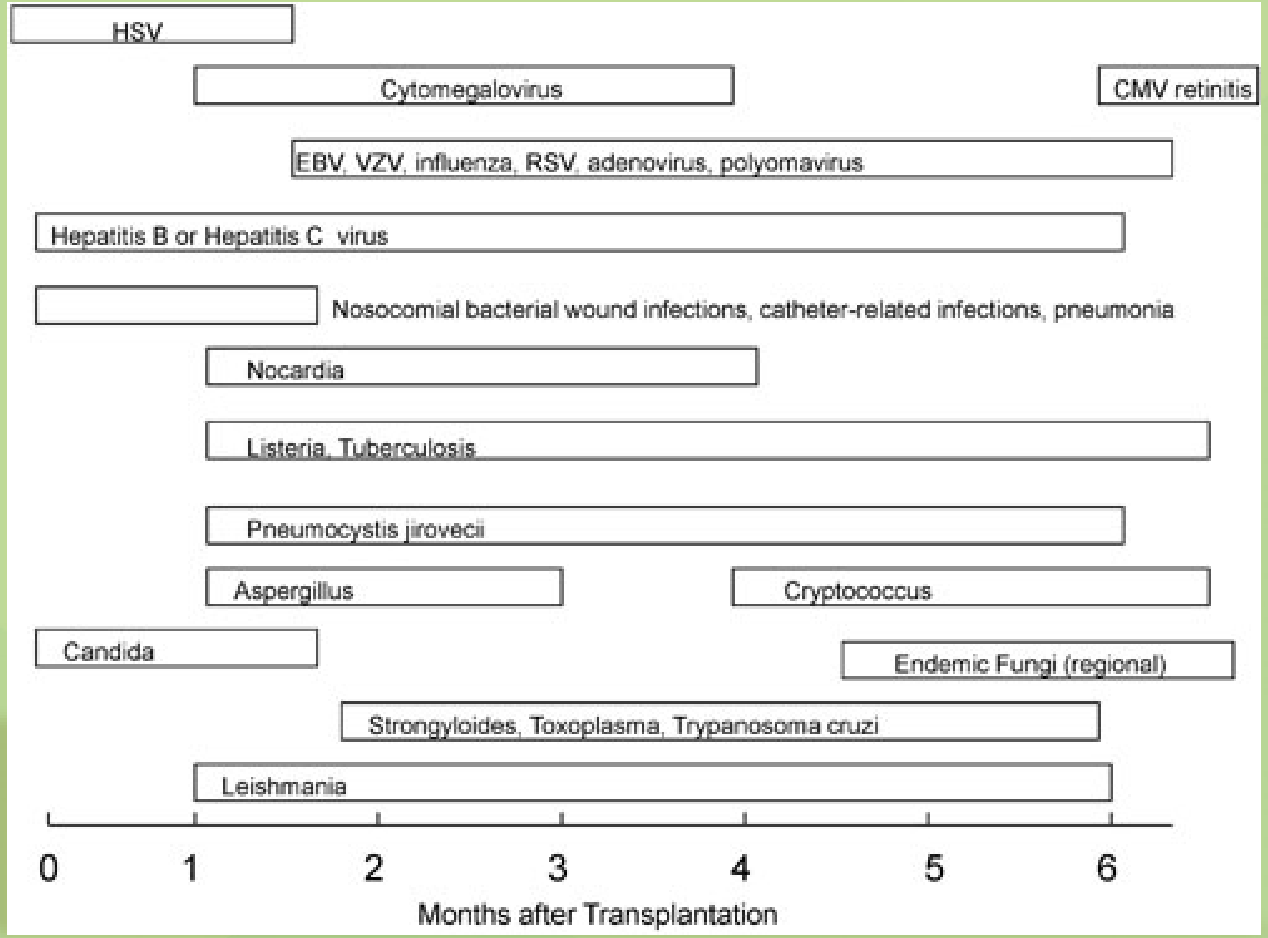
Timeline of opportunistic infections after allogeneic hematopoietic cell transplantation

Microbiol Spectr. 2016;4(4):10

Creighton University

DIRECT Approach to Early Diagnosis

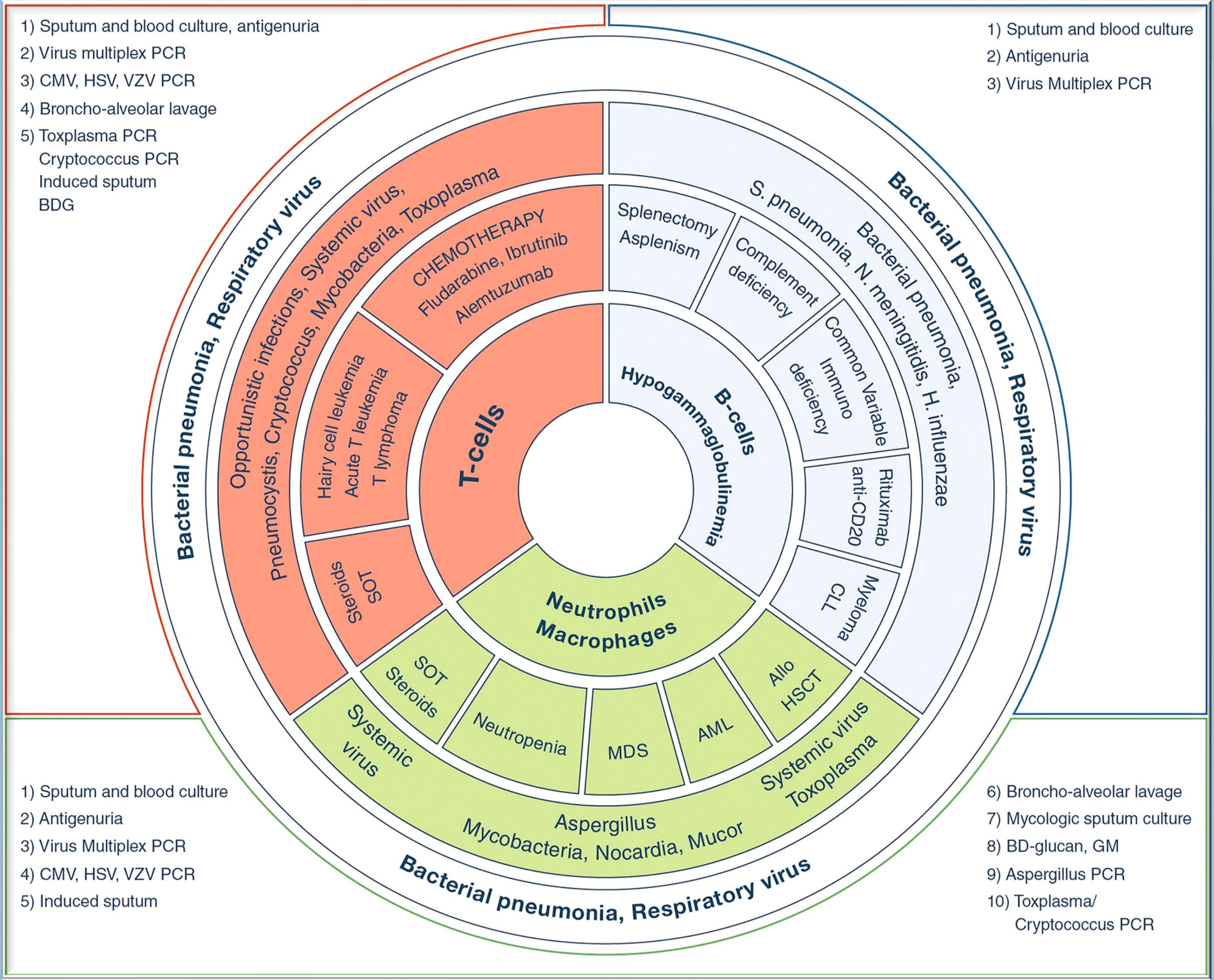
Delay:
Time since immune suppression



Timeline of infections after solid organ transplantation

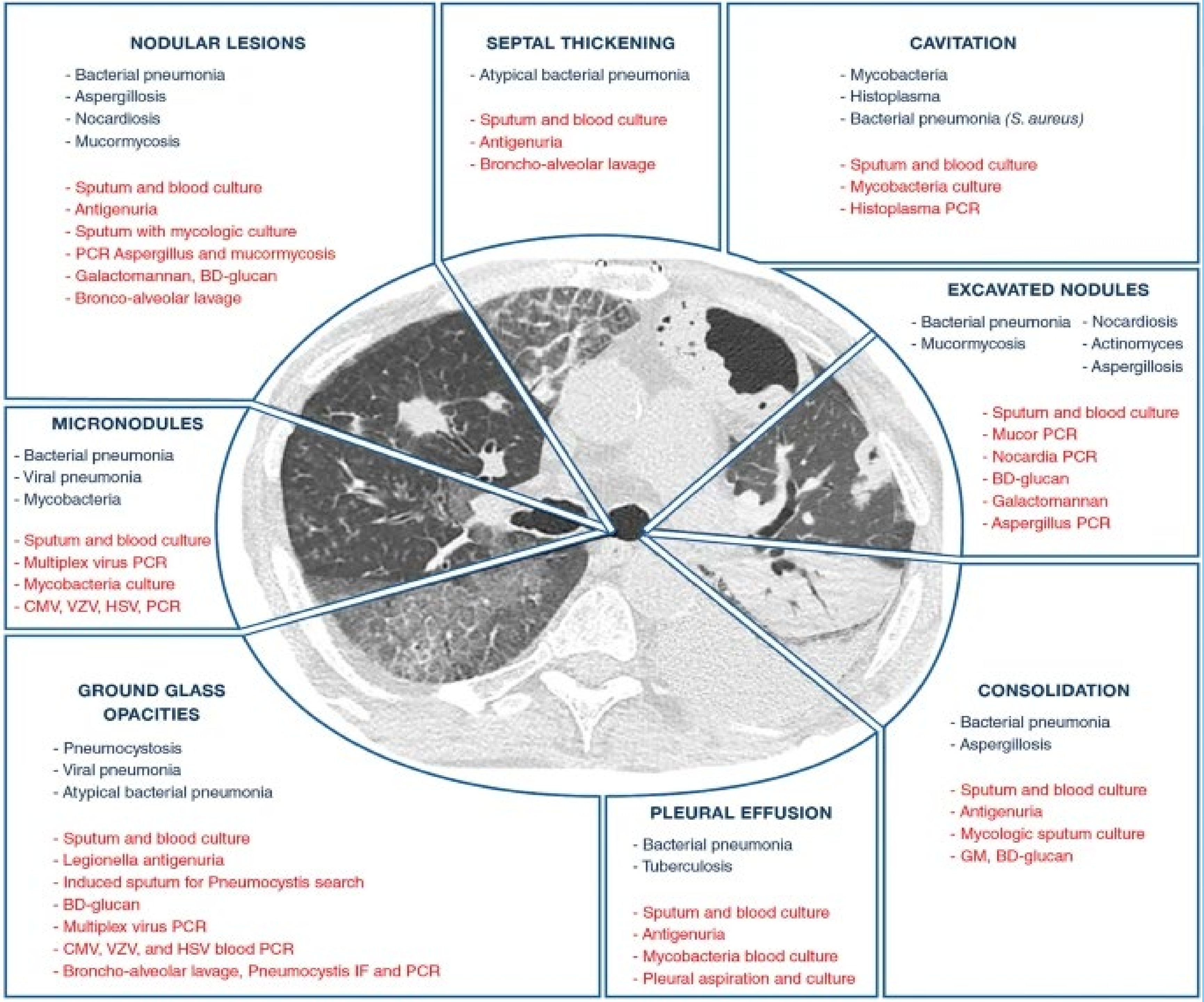
Microbiol Spectr. 2016;4(4):10

Immune deficiency



Creighton UNIVERSITY

Radiological Changes in Critical Illness



Creighton UNIVERSITY

Early Diagnostics of Common Infections in ICU

Genitourinary

Urine
- Multiplex NAAT for bacteria, fungi and resistance markers

Bloodstream

Positive Blood Culture
- MALDI-TOF
- Gel electrofiltration and FISH

Whole Blood
- Multiplex NAAT for bacteria Multiplex NAAT for *Candida* species
- Cell-free microbial nucleic acid sequencing (Karius)

Respiratory

Nasopharyngeal Swab
- Single target PCR for viruses
- Single target PCR for bacteria (specifically MRSA)
- Multiplex NAAT for viruses and atypical bacteria

Sputum and Endotracheal Aspirate
- Multiplex NAAT for viruses and bacteria +/- resistance markers

Bronchoalveolar Lavage
- Multiplex NAAT for viruses and bacteria +/- resistance markers
- Single target PCR for viruses and bacteria

Gastrointestinal

Stool
- EIA testing for GDH and Toxin A + B for *C.difficile*
- Single target NAAT for *C.difficile*
- Multiplex NAAT for enteric pathogens

Intraabdominal fluid collection
- 16s rRNA
- Metagenomic sequencing

Neurological

Cerebrospinal fluid
- Pneumococcal antigen
- Latex agglutination
- Multiplex NAAT

Clin Chest Med 43 (2022) 401–410

Creighton University

Diagnostics for Pulmonary Infections

- Point prevalence study of more than 13,000 ICU patients revealing pulmonary source of infection in 64% cases
- Mortality associated with pneumonia requiring ICU admission ranges from 15% to 50%
- Rapid diagnostic test with turn around time of around 2 hr
- Upper respiratory tract testing is not sufficient to diagnose LRT viral infection in critically ill patients

Clin Chest Med 43 (2022) 401–410

Creighton UNIVERSITY

Rapid Diagnostics for Pulmonary Infections

	BioFire FilmArray Pneumonia Panel
Specimen	Bronchoalveolar lavage Sputum Endotracheal aspirate
Bacterial Targets	18
Viral Targets	8
Resistance Markers	7
Quantitation	Semiquantitative
Overall Weighted Sensitivity	96.2% (96.3% for sputum)
Specificity	98.3% (97.2% for sputum)
Turnaround Time	1.5 h
Technology	Multiplex PCR

ANTIMICROBIAL RESISTANCE GENES:

Carbapenemases:
- IMP
- KPC
- NDM
- OXA-48-like
- VIM

ESBL:
- CTX-M

Creighton UNIVERSITY

Rapid Diagnostics for Pulmonary Infections

Rapid NAAT based MRSA testing & empirical anti-MRSA therapy:

- NPV of MRSA nasal swab is noted as high as 99.2% but PPV ranging from 17% to 35%.
- MRSA PCR tests on BAL samples with sensitivity of 95.7%, specificity of 98.2%, and negative predictive value of 99.6% for detection of culture positive MRSA pneumonia
- RCT of antibiotic de-escalation based on the results of MRSA PCR tests on BAL samples compared with usual care revealed no adverse effects, shorter duration of anti-MRSA therapy with a trend to lower hospital mortality

Chest 2019;155(5):999–1007

Creighton UNIVERSITY

Rapid Diagnostics for Bloodstream Infections

When should we suspect bloodstream infection?

- Disruption of anatomic barriers
- Presence of central venous catheters
- Immunosuppression
- Dialysis
- Parenteral nutrition

Rapid Diagnostics for Bloodstream Infections

NAATs

- From positive blood cultures include BioFire FilmArray BCID
- From blood directly, like T2-Biosystems NAATs and do not require positive blood culture
- Need target-specific primers

Next-generation sequencing (Karius test)

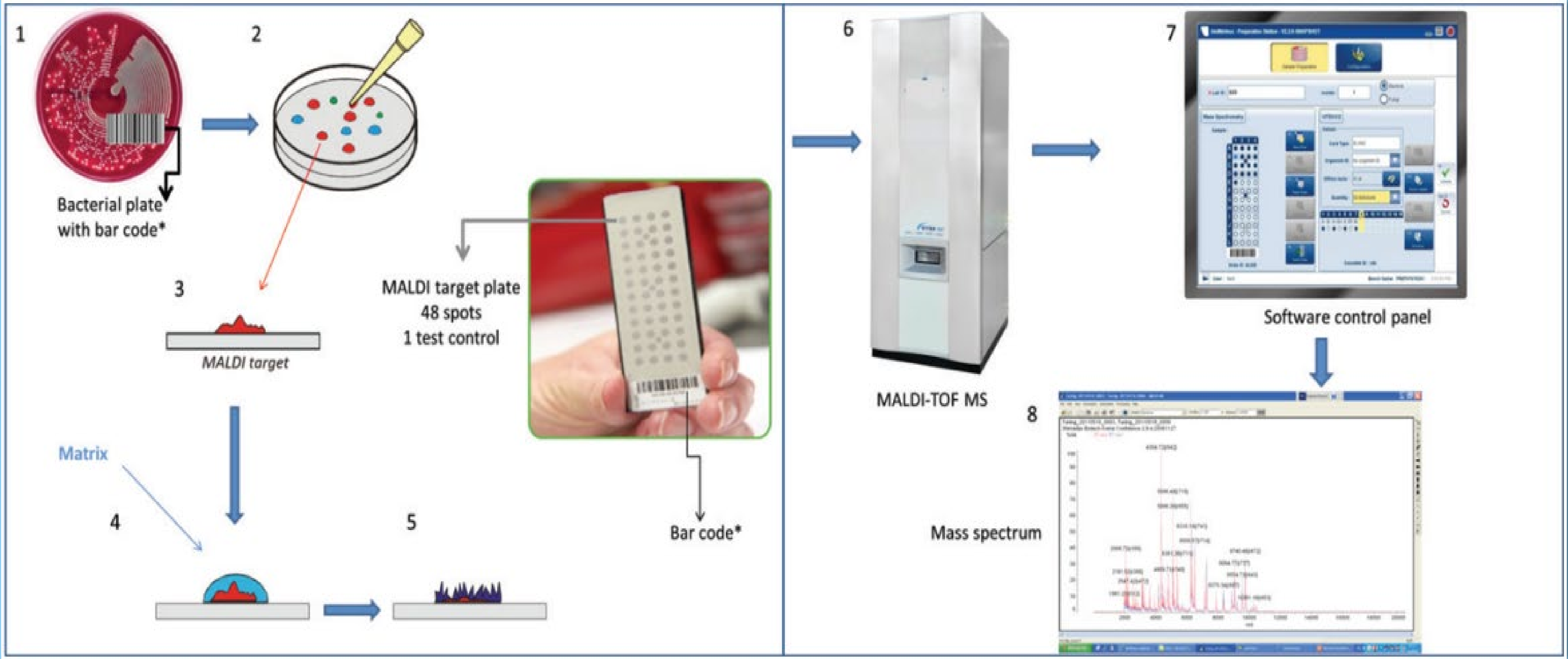
- Capable of detecting more than 1000 bacteria, viruses, and fungi by sequencing of cell-free DNA, with results potentially available within 24 hours
- Send-out test and associated lag time
- Febrile Neutropenia or culture negative endocarditis

Clin Chest Med 43 (2022) 401–410

Creighton UNIVERSITY

Rapid Diagnostics for Bloodstream Infections

Matrix-assisted laser desorption ionization–time of-flight mass spectrometry (MALDI-TOF)



MALDI-TOF helps critically ill patients?

- Decrease time to organism identification by 1.5 days
- Identifying known and unknown organisms, unlike PCR where primers are required to identify organism

Study	Percentage (No.) organisms correctly detected by MALDI-TOF MS	
	Genus level	Species Level
Gram negative bacteria		
Faron etal., 2015 [29]	99.8% (2258/2263)	98.2% (2222/2263)
Gamer etal., 2013 [30]	92.5% (357/386)	91.7% (351/386)
Gram positive bacteria		
Rychert etal., 2013 [31]	95.5% (1094/1146)	92.8% (1063/1146)
Gamer et al., 2013 [30]	92.5% (245/265)	91.7% (243/265)
Anaerobic bacteria		
Garner etal.,	92.5% (602/651)	91.2% (591/651)

Creighton UNIVERSITY

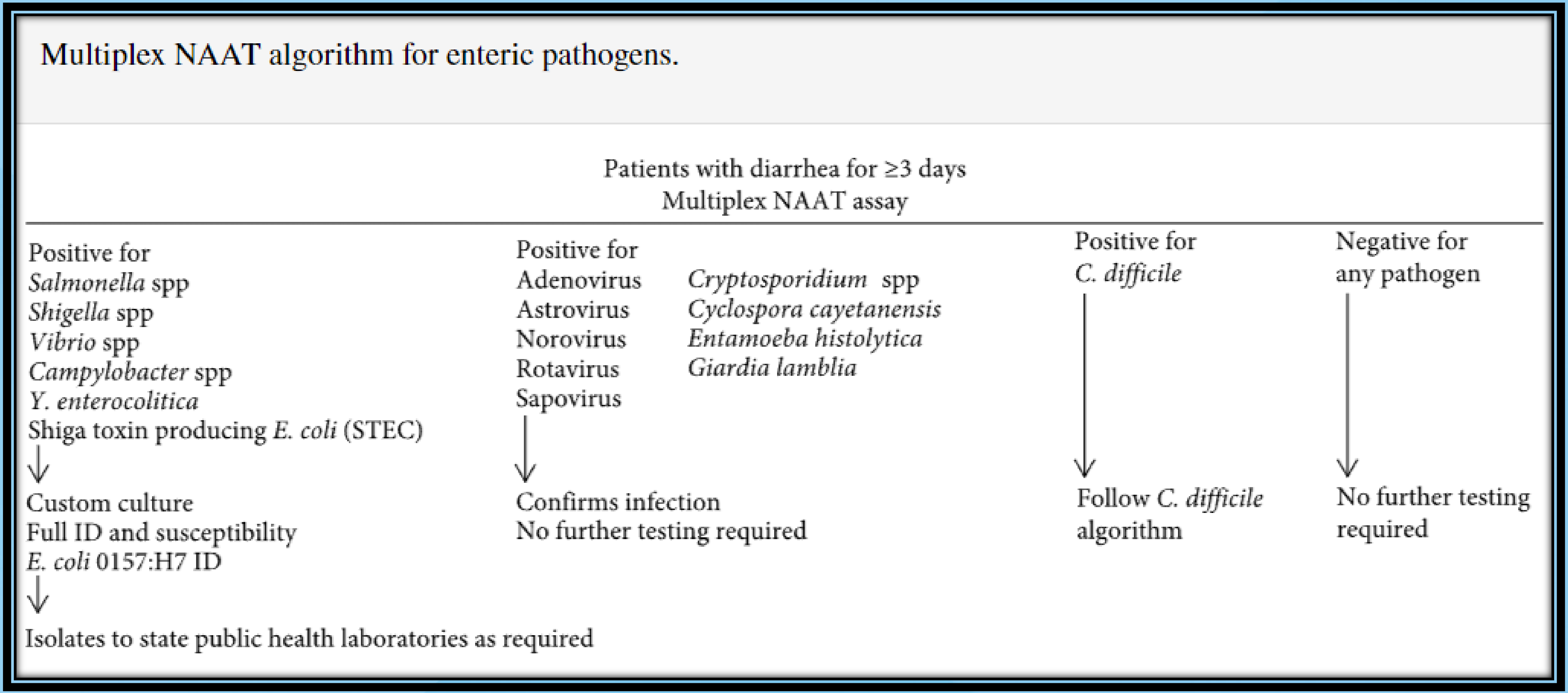
Rapid Diagnosis of Intraabdominal Infections

- Septic Shock due to cholecystitis, cholangitis, infected pancreatitis, visceral perforation and resulting intra-abdominal fluid collections, infected grafts or mesh and peritonitis
- 16s rRNA sequencing and/or metagenomic shotgun sequencing not much helpful on intrabdominal fluid collections
- Multiplex gastrointestinal NAATs on stool sample with turn around time of 2-5 hrs, having 54% detection rate as compared to 18% with conventional culture
- CDI remains most common acute diarrheal illness in ICU with 20% of cases having fulminant disease

Clin Chest Med 43 (2022) 401–410

Creighton UNIVERSITY

Rapid Diagnosis of Intraabdominal Infections

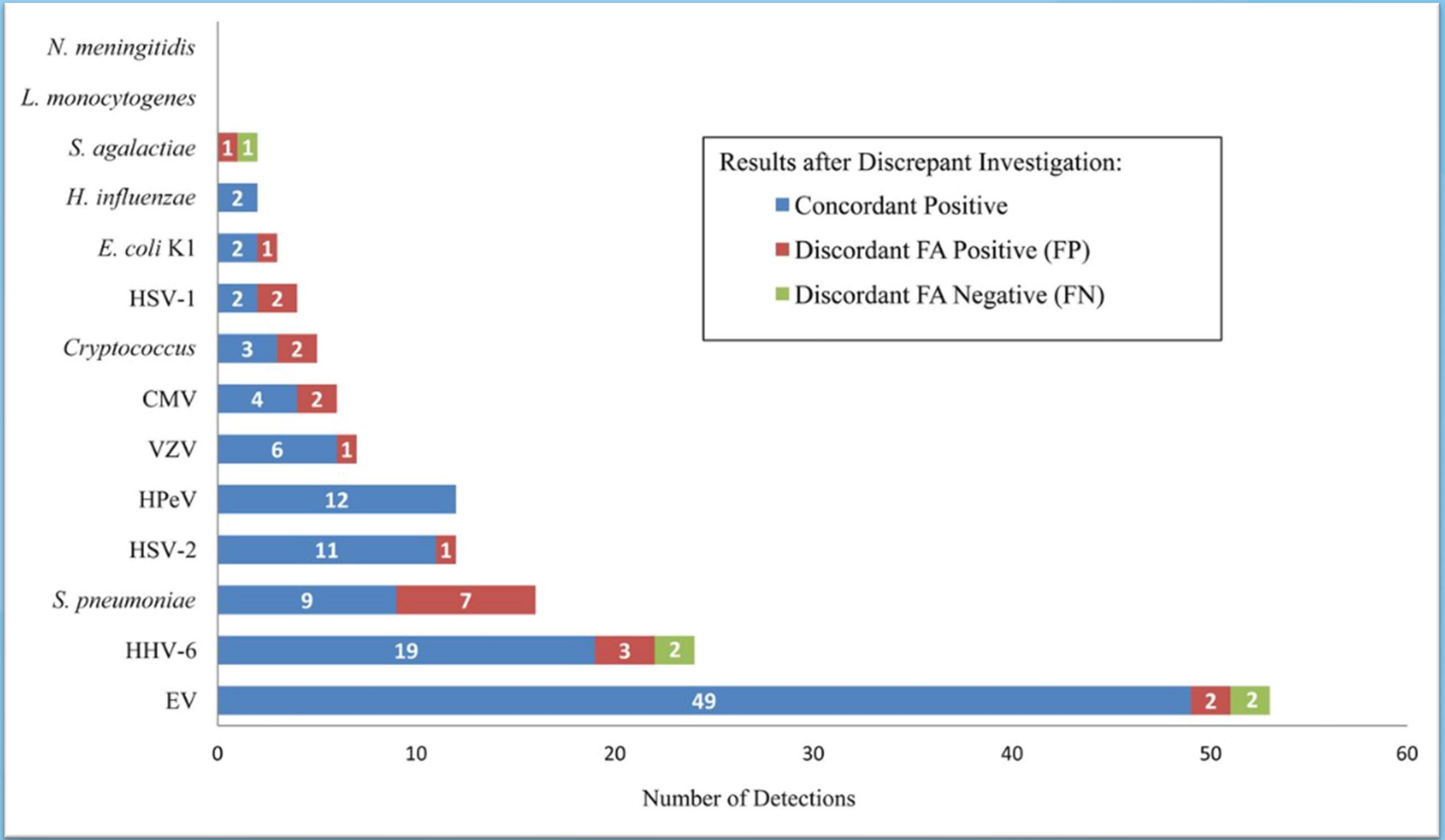


Clin Chest Med 43 (2022) 401–410

Rapid Detection of Meningitis

- Study based on 21,840 individual FilmArray ME analyte tests

- Overall percentage of agreement with comparator test for positive targets was 69.5% (98/141), agreement for the negative targets was >99.9% (21,693/21,699)



Journal of Clinical Microbiology Vol. 54(9), pp. 2251-2261

Creighton UNIVERSITY

Rapid Detection of Meningitis

Radiographic Finding	Pathogen or Condition	Comments
Frontal lobe involvement	*Naegleria fowleri* (primary amoebic meningoencephalitis)	Seasonal, associated with freshwater exposure and fulminant infection
Temporal lobe involvement	HSV-1	Often asymmetric, HSV-1 is part of core testing regardless of MRI findings
	Autoimmune limbic encephalitis	Often symmetric, involving the mesial temporal lobes
	HHV-6	Rare condition presenting shortly after stem cell transplantation; false positives may occur due to chromosomal integration or latency
Deep gray matter (basal ganglia or thalamus) involvement	West Nile virus	Part of core testing during appropriate season regardless of MRI findings
	Japanese encephalitis virus	Associated with travel to Asia, emerging infection in Australia
Brainstem involvement	*Listeria monocytogenes*	Lower brainstem (“rhombencephalitis”), can occur in immunocompetent individuals
	Enteroviruses	EV-A71, and less commonly other EV; seen primarily in children
Cerebellar involvement	EBV	Associated with acute infection, more common in children
	VZV	CSF PCR part of core testing, typically seen in acute infection (chickenpox)

Clinical Infectious Diseases, 2023;, ciad306

Creighton UNIVERSITY

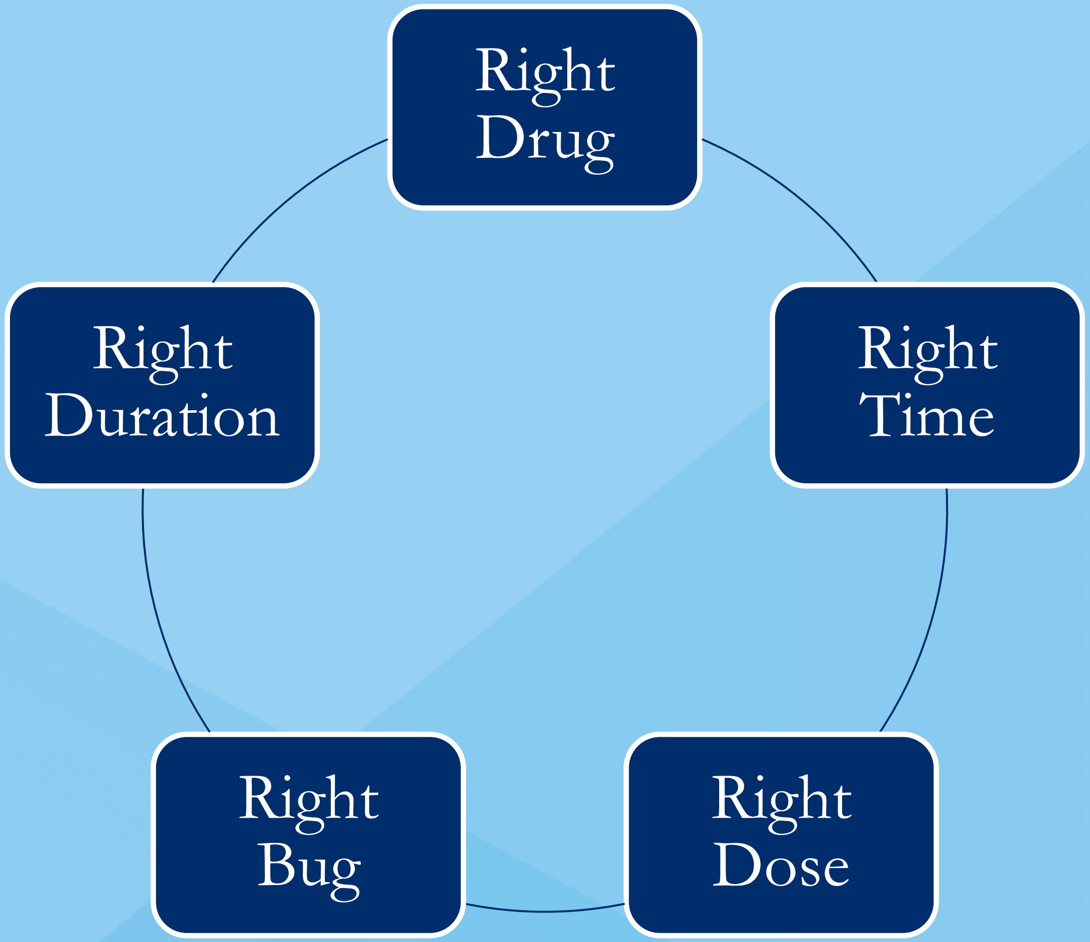
Acute Ischemic Changes and CNS Infection in Critical Illness

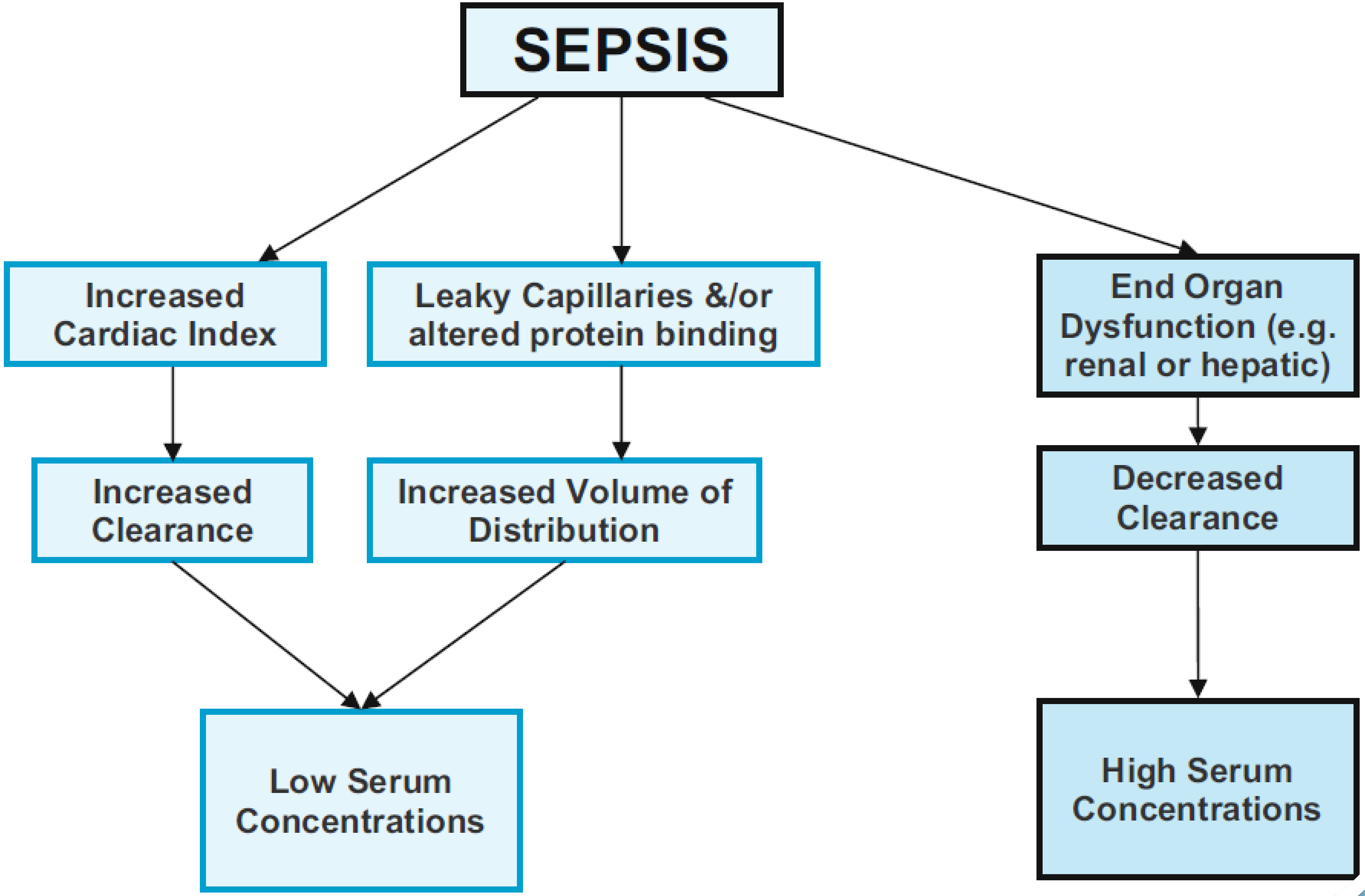
VZV	VZV-associated vasculopathy can occur in immunocompetent and immunocompromised individuals
Syphilis	Acute or chronic presentation
Fungal infections	Aspergillus and mucormycosis are particularly angioinvasive
Rickettsia rickettsii	RMSF "starry sky" pattern, especially in children
Tuberculosis	Deep portions of the brain

Clinical Infectious Diseases, 2023;, ciad306

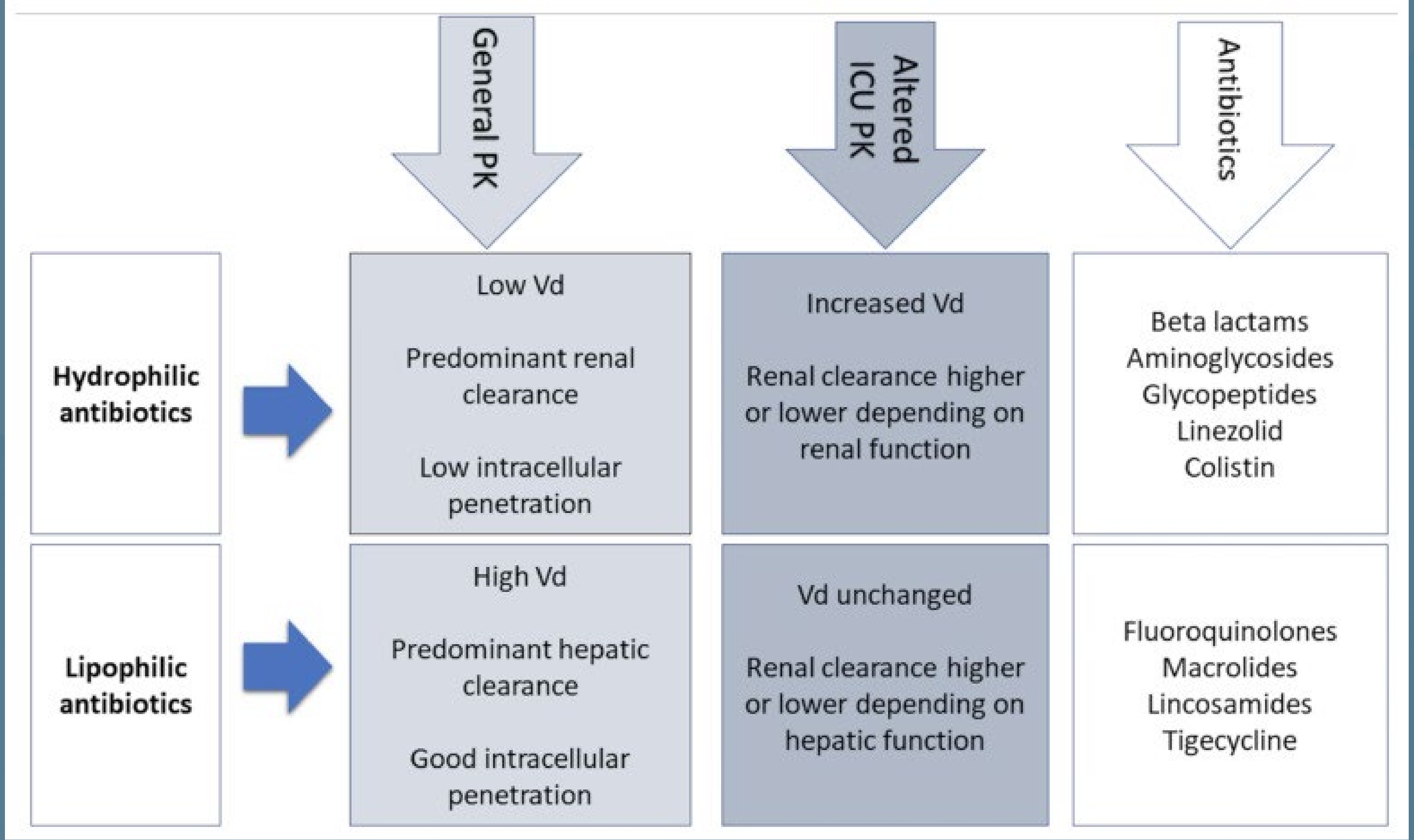
Creighton UNIVERSITY

What is Appropriate Antibiotic?



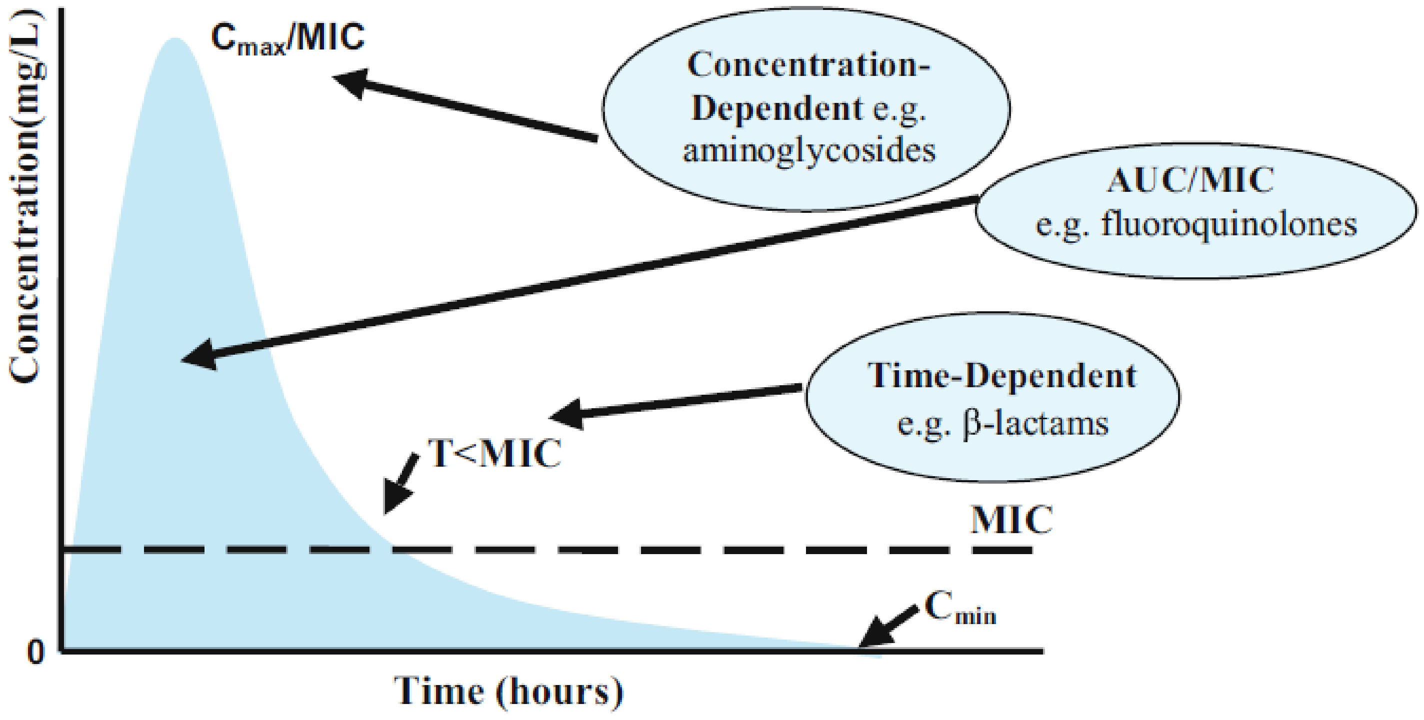


Creighton UNIVERSITY



Application of PK-PD in medicine has been associated with better clinical outcome, suppression of resistance, and optimization of antibiotic use

Creighton UNIVERSITY

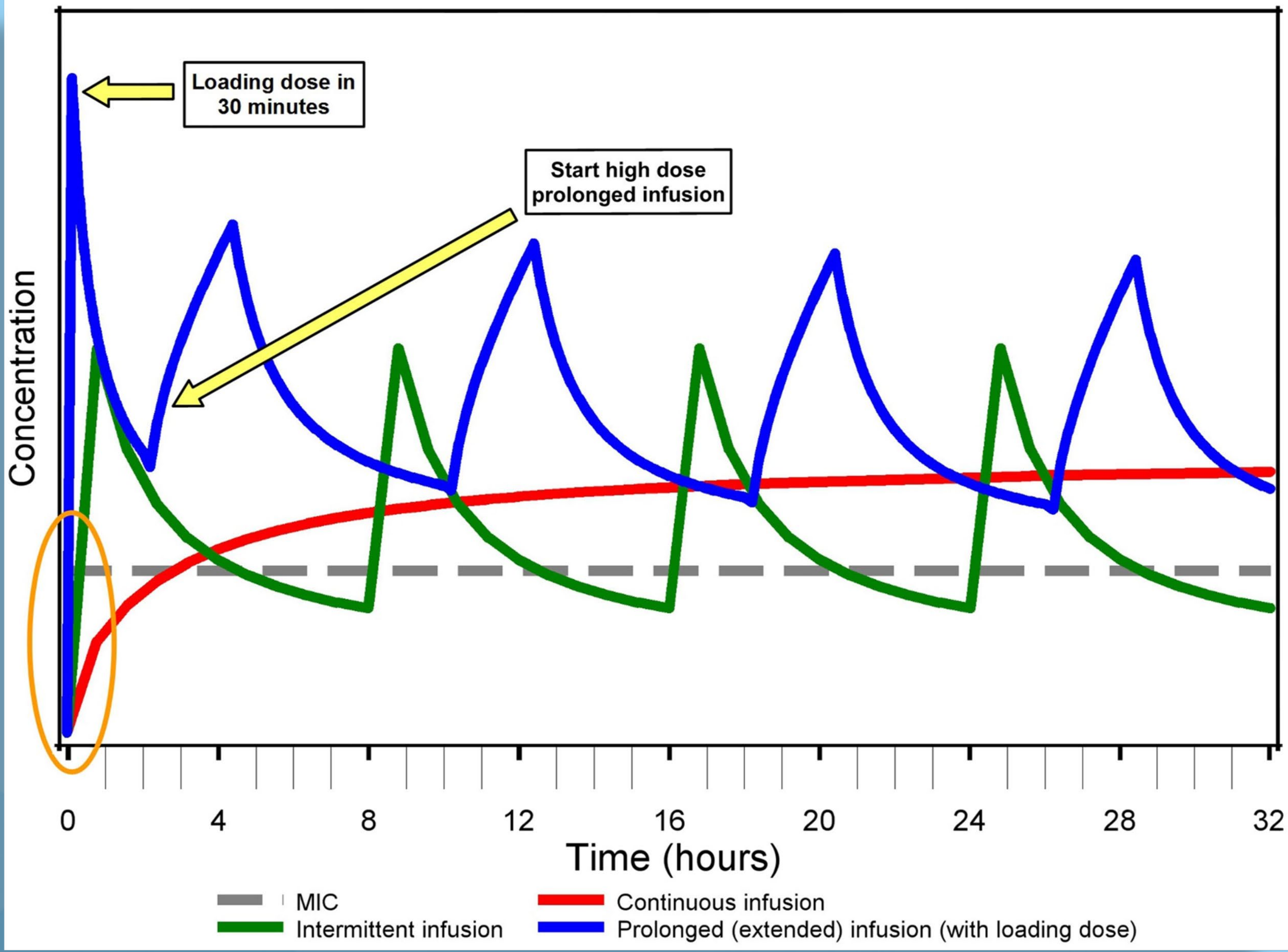


Antibiotics	Aminoglycosides Metronidazole Fluoroquinolones Telithromycin Daptomycin Quinupristin/dalfopristin	Fluoroquinolones Aminoglycosides Azithromycin Tetracyclines Glycopeptides Tigecycline Quinupristin/dalfopristin Linezolid	β-Lactams Carbapenems Linezolid Erythromycin Clarithromycin Lincosamides
PD kill characteristics	Concentration-dependent	Concentration-dependent with time dependence	Time-dependent
Optimal PD parameter	C_{max}: MIC	AUC_{0-24}: MIC	$T >$ MIC

Creighton UNIVERSITY

β-lactam Antibiotics for Critically Ill Patients

- % fT > MIC has been considered as PK-PD index that best predicts the relationship between antibiotic exposure and killing for beta-lactam antibiotics



PK-PD model with different modes of administration

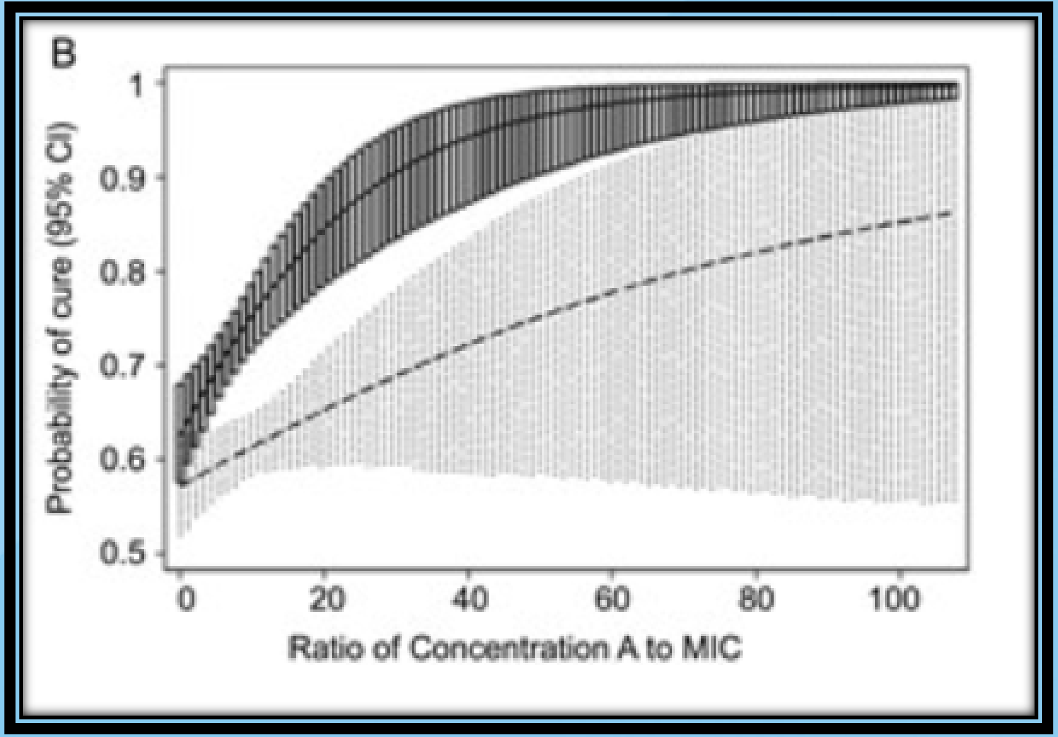
Creighton UNIVERSITY

Open Forum Infectious Diseases, 10(7) July 2023

β-lactam Antibiotics for Critically Ill Patients

DALI Study: Defining Antibiotic Levels in Intensive Care Unit Patients

- Prospective, multinational PK point-prevalence study including 8 β-lactam antibiotics
- 384 patients (65% males) across 68 hospitals with median APACHE II score of 18
- Of the 248 patients treated for infection, 16% did not achieve 50% $f\,T_{>MIC}$ and these patients were 32% less likely to have a positive clinical outcome



Effect of PK/PD ratio at 50% of the dosing interval (ratio A) in interaction with APACHE II score on probability of positive clinical outcome for patients not receiving renal replacement therapy

Clin Infect Dis. 2014;58(8):1072-1083

Creighton UNIVERSITY

Issue of the Tissue Distribution

Drugs	Piperacillin (Pip/Tazo)	Ceftazidime	Ceftriaxone	Cefepime	Meropenem (Mer/Vab)
Daily doses	−4.5 g q6h −22 g CI	−6 g CI −20 mg/kg q8h −2 g q8h	−1–2 g	−2 g q12h −4 g CI	−1 g q8h −2 g q8h EI or CI −[2 + 2 g q8h, 3 h-inf]
CNS		0.24X (2 h)	<0.1X (2 h)		0.21X (2.5 h)
CSF	<0.1X			0.3–2.14X [A] 0.03–1.14X [B]	0.08X
Lung tissue	0.28 (0.5 h)–0.92X (1.5 h)		0.45X (1 h)	>0.8X (0.5 h)	
ELF	[0.4–0.5X/0.65–0.85X]	0.21–0.44X 0.21X		1X	0.25–0.3X [0.52–1.85X/0.44–0.74X]
Bronchial secretion	0.02–0.25X	0.76X	0.02X		
Bronchial mucosa				0.6X	
Abdomen	0.43–0.53X [C]	0.35–0.56X [D]	0.09X [E]	0.51X	0.74X [D]
Bone	0.1–0.4X 1X [0.5/0.4X] [F]	0.1–0.3X (0.5 h)	0.48X (1.5 h) 0.1–0.4X (2–2.5 h)	0.87–1.06X	0.4–1X
Skin	0.6–0.95X		0.53X (4 h)	>1X (2 h)	>0.8X

Antibiotics. 2022; 11(9):1164.

Creighton University

Issue of the Tissue Distribution

- Desired tazobactam concentration in CSF is ~4 mg/liter, but currently utilized doses of tazobactam in commercially available combination formulation may not be effective in treating CNS infection

- Ceftriaxone is highly protein bound in the serum (83–96%), likely leading to the delayed entry in CSF, but provides benefit through a long half-life in both the serum and CSF providing higher level of AUC_{CSF}:AUC_{serum} ratio

- BBB penetration of ceftriaxone was unaffected by the use of steroids and has greater bactericidal activity in the CSF compared to ampicillin

Antibiotics (Basel). 2022;11(12):1843

Understanding Antimicrobial Resistance and Critical Illness

Inducible Resistance of Bacterial Strain

- Exposure to antibiotics triggers increased production of Amp-C b-lactamase enzymes and development of de-repressed resistant mutants
- *Enterobacter cloacae*, *Klebsiella aerogenes* (formerly *Ent erobacter aerogenes*), and *Citrobacter freundii*

Resistant Strains with Local Epidemic Outbreak

- Infection control
- Impact on the antibiotic policy of ICU
- Major effect on the clinical course of patients with intermediate degrees of illness severity

Long ICU Stay, Broad Spectrum ABx, High Severity Score

- Multi-resistant strains
- (MRSA, *P. aeruginosa, A. baumannii*)
- Marker of severity
- Although it has a low effect on the final outcome of patient or on the antibiotic policy of ICU

Understanding Antimicrobial Resistance and Critical Illness

CHI Health Laboratories Antibiogram January - December 2022 Data are Percent Susceptible

GRAM POSITIVE ORGANISM	# of isolates	Ampicillin	Cefazolin (1)	Ceftriaxone	Ceftriaxone (2)	Ceftriaxone (3)	Clindamycin (4)	Erythromycin (4)	Gentamicin (5,6)	Levofloxacin	Minocycline	Nitrofurantoin (7)	Oxacillin	Penicillin	Penicillin (2)	Penicillin (3)	Trimethoprim/Sulfamethoxazole	Tetracycline	Vancomycin
Enterococcus faecalis	1312	99							86		27	99		99					99
Enterococcus faecium	221	21							92			46		21					56
Staphylococcus aureus (Total)	3373		68				75	50			98		68				96		100
Staphylococcus aureus (MSSA)	2283		100				76	66			98		100				97		100
Methicillin Resistant S. aureus (MRSA)	1090		0				72	16			97		0				93		100
Staphylococcus epidermidis	263		40				63	32			97		40				72		100
Staphylococcus hominis	78		65				71	48			100		65				83		100
Staphylococcus lugdunensis	132		95				90	88			100		95				99		100
Streptococcus anginosus group (8)	227			98			76	68		100				99					100
Streptococcus pneumoniae	139				95	99		67		100					87	98			100

Understanding Antimicrobial Resistance and Critical Illness

Risk of MDR pathogens:

- Proven infection or colonization with antibiotic-resistant organisms within preceding year
- Local prevalence of Abx-resistant organisms in ICU
- Broad-spectrum Abx use within preceding 90 days
- Travel to a highly endemic country within the preceding 90 days

CHI Health Laboratories Antibiogram   January - December 2022 Data are Percent Susceptible

GRAM NEGATIVE ORGANISM	# of isolates	Amikacin	Ampicillin	Ampicillin/Sulbactam	Cefazolin	Cefepime	Ceftriaxone	Ciprofloxacin	Ertapenem	Gentamicin	Levofloxacin	Meropenem	Nitrofurantoin (1)	Piperacillin/Tazobactam	Tobramycin	Trimethoprim/ Sulfamethoxazole
Acinetobacter baumannii	*Insufficient isolates*															
Citrobacter freundii	183					100		91	100	98	88		92	87	98	95
Citrobacter koseri	197				99	99	99	98	98	99	98		87	100	99	99
Enterobacter cloacae complex	372					97		95	90	99	91		41	79	98	90
Escherichia coli	14804		57	67	89	95	93	80	99	93	75		97	94	93	78
Klebsiella (Enterobacter) aerogenes	325					99		99	98	99	93		12	79	100	99
Klebsiella oxytoca	433			65	62	96	89	93	100	95	92		84	91	97	91
Klebsiella pneumoniae	2096			91	92	95	93	91	100	96	88		26	96	96	91
Morganella morganii	85			16		98		69	100	82	68		0	99	91	77
Proteus mirabilis	1304		81	93	92	96	96	74	100	93	74		0	99	94	79
Proteus vulgaris	44			59		98	77	100	95	100	98		0	100	100	96
Providencia rettgeri	39			53		100		97	94	100	95		0	97	100	90
Providencia stuartii	*Insufficient isolates*															
Pseudomonas aeruginosa	1253	100				92		82		94	77	94		91	98	
Serratia marcescens	165					100		94	99	100	90		0		100	99
Stenotrophomonas maltophilia (2)	84										84					84

Creighton UNIVERSITY

IDSA 2023 Guidance on the Treatment of Antimicrobial Resistant Gram-Negative Infections

Determining empiric treatment for patient based on :

(1) Previous organisms identified from patient and associated antibiotic susceptibility data in the last six months

(2) Antibiotic exposures within past 30 days

(3) Local susceptibility patterns for most likely pathogens.

Clinical Infectious Diseases, published: 18 July 2023

IDSA 2023 Guidance on the Treatment of Antimicrobial Resistant Gram-Negative Infections

What are preferred antibiotics for the treatment of pyelonephritis and complicated UTI caused by ESBL-Enterobacterales?

- Carbapenems are preferred agents, when resistance or toxicities prevent use of TMP-SMX or fluoroquinolones, or early in the treatment course if a patient is critically ill

What are preferred antibiotics for treatment of infections outside of urinary tract caused by ESBL-Enterobacterales?

- Carbapenem recommended as first-line treatment of ESBL infections outside of urinary tract
- Meropenem rather than ertapenem, as initial therapy in critically ill patients with ESBL-E due to known pharmacokinetic alterations in patients with critical illness resulting in significant decrease in serum half-life of Ertapenem

Clinical Infectious Diseases, published: 18 July 2023

Creighton University

IDSA 2023 Guidance on the Treatment of Antimicrobial Resistant Gram-Negative Infections

What are preferred antibiotics for treatment of pyelonephritis and complicated UTI caused by CRE?

- Ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam, or cefiderocol can be preferred treatment options for pyelonephritis and cUTIs in critical illness

What are preferred antibiotics for treatment of infections outside of urinary tract caused by CRE ?

- Ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-cilastatin-relebactam are preferred treatment options

Clinical Infectious Diseases, published: 18 July 2023

Creighton UNIVERSITY

Understanding Antimicrobial Resistance and Critical Illness

Agent	KPC-producer	NDM-producer	OXA-48-like-producer	Carbapenem-resistant *Pseudomonas aeruginosa*	Carbapenem-resistant *Acinetobacter baumannii*	*Stenotrophomonas maltophilia*
Aztreonam-avibactam	Green	Green	Green	Yellow	Red	Green
Cefiderocol	Green	Green	Green	Green	Green	Green
Ceftazidime-avibactam[1]	Green	Red	Green	Yellow	Red	Red
Ceftolozane-tazobactam[1]	Red	Red	Red	Yellow	Red	Yellow
Eravacycline[1,2]	Green	Green	Green	Red	Green	Green
Fosfomycin (intravenous)	Yellow	Yellow	Yellow	Yellow	Red	Red
Imipenem-relebactam[3]	Green	Red	Yellow	Green	Red	Red
Meropenem-vaborbactam[1]	Green	Red	Red	Red	Red	Red
Plazomicin[1,4]	Green	Yellow	Green	Yellow	Red	Red
Polymyxin B[1,5] or Colistin[1,5]	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow
Tigecycline[1,2]	Green	Green	Green	Red	Green	Green

Antimicrobial activity against carbapenem-resistant organisms

Green: Susceptibility anticipated to be >80%
Yellow: Susceptibility anticipated to be 30% to 80%
Red: Intrinsic resistance or susceptibility anticipated to be <30%

J Pediatric Infect Dis Soc. 2019;8(3):251-260.

Creighton UNIVERSITY

Take Home Points:

- Understanding the underlying immune deficiency and thorough clinico-radiological evaluation can guide diagnostic strategy by targeting the most likely infectious agents in critically ill patient

- Timely utilization of novel non-invasive diagnostic tools can avoid clinical deterioration by early detection of pathogens

- Understanding of PK-PD and antimicrobial resistance patterns can guide appropriate antimicrobial dosing

Questions and Comments

Creighton
UNIVERSITY