Antimicrobial Therapy Challanges in critically ill patients

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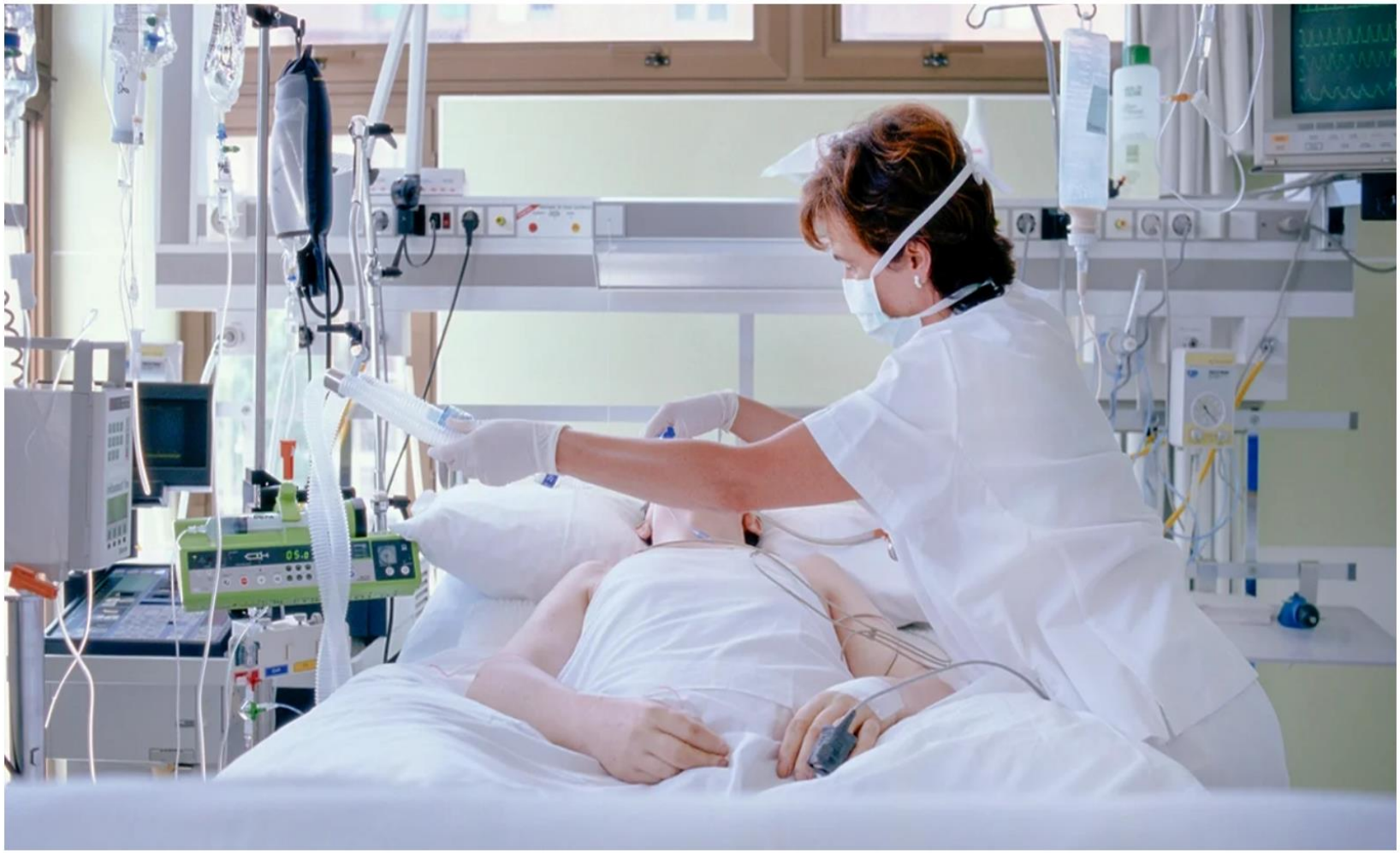
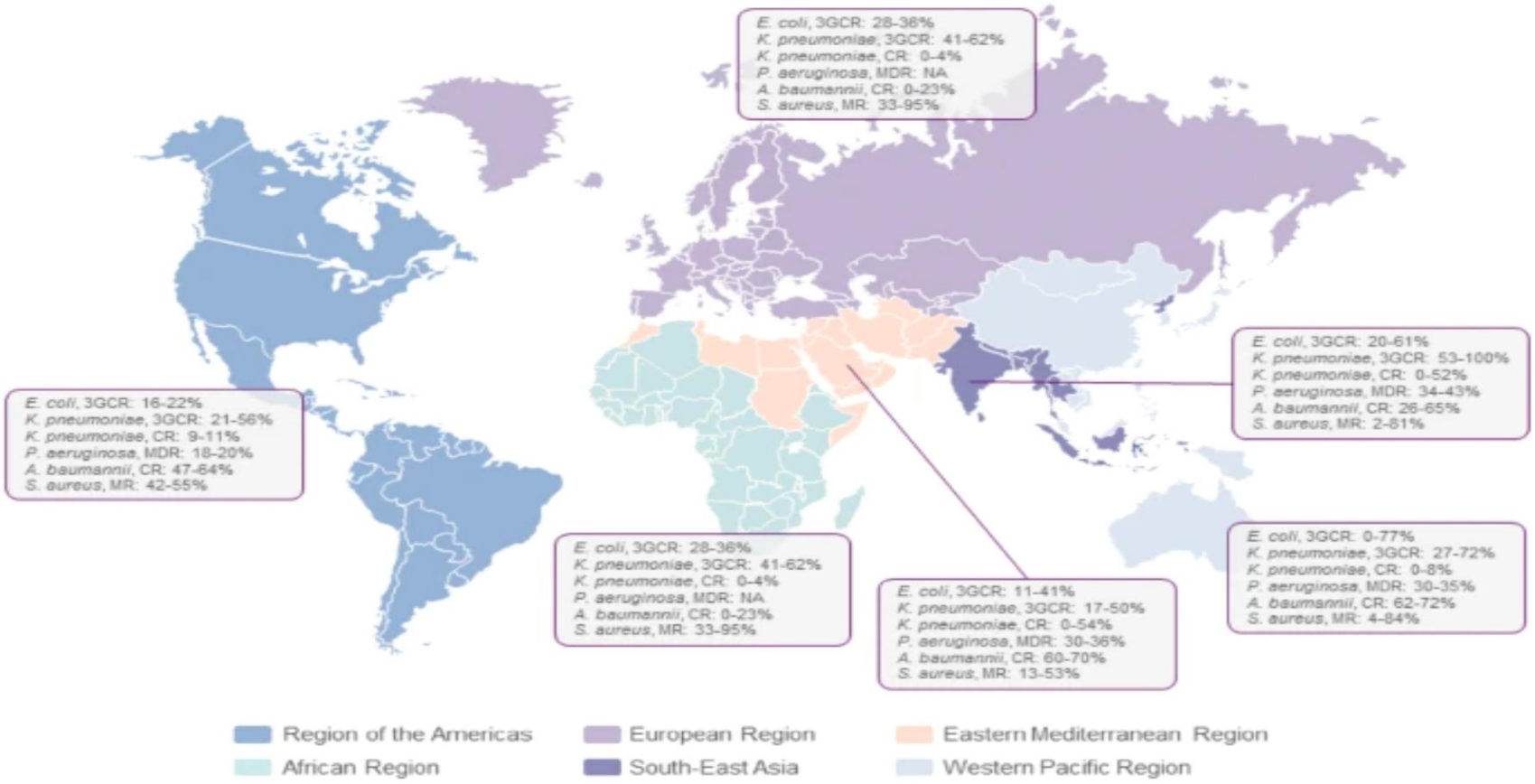
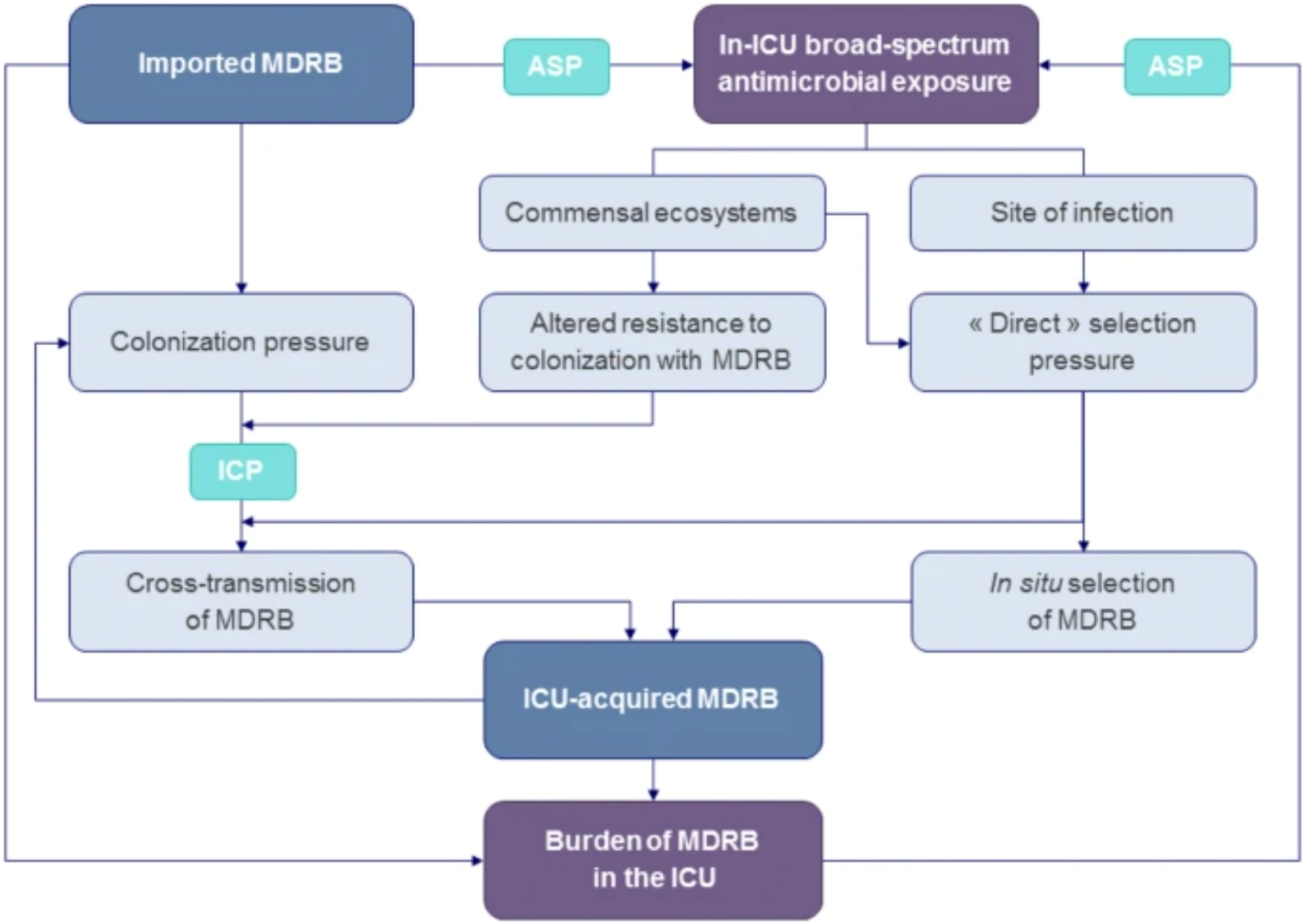
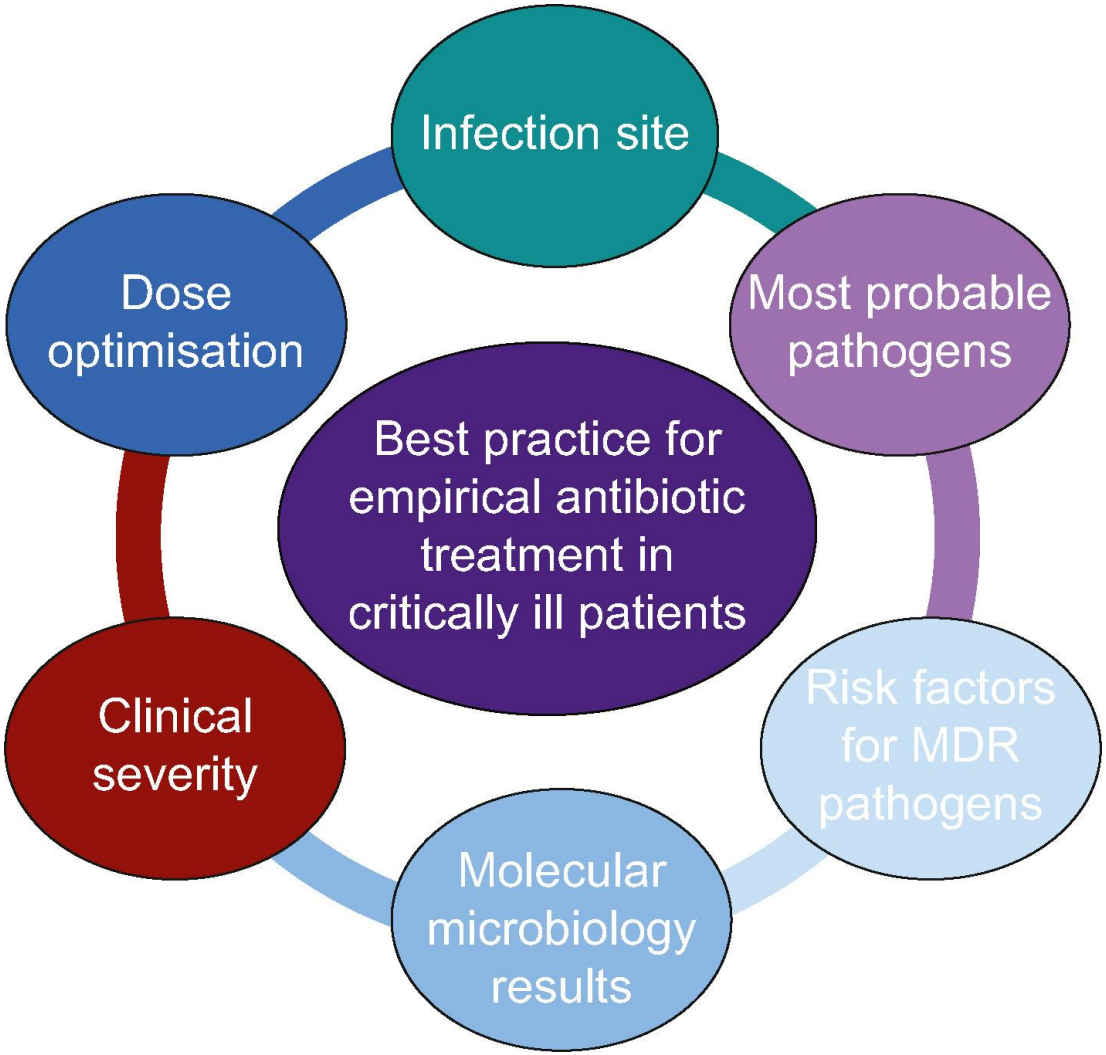



E. coli, 3GCR: 28-38%
K. pneumoniae, 3GCR: 41-62%
K. pneumoniae, CR: 0-4%
P. aeruginosa, MDR: NA
A. baumannii, CR: 0-23%
S. aureus, MR: 33-95%
E. coli, 3GCR: 16-22%
K. pneumoniae, 3GCR: 21-56%
K. pneumoniae, CR: 9-11%
P. aeruginosa, MDR: 18-20%
A. baumannii, CR: 47-64%
S. aureus, MR: 42-55%
E. coli, 3GCR: 20-61%
K. pneumoniae, 3GCR: 53-100%
K. pneumoniae, CR: 0-52%
P. aeruginosa, MDR: 34-43%
A. baumannii, CR: 26-65%
S. aureus, MR: 2-81%
E. coli, 3GCR: 28-36%
K. pneumoniae, 3GCR: 41-62%
K. pneumoniae, CR: 0-4%
P. aeruginosa, MDR: NA
A. baumannii, CR: 0-23%
S. aureus, MR: 33-95%
E. coli, 3GCR: 11-41%
K. pneumoniae, 3GCR: 17-50%
K. pneumoniae, CR: 0-54%
P. aeruginosa, MDR: 30-36%
A. baumannii, CR: 60-70%
S. aureus, MR: 13-53%
E. coli, 3GCR: 0-77%
K. pneumoniae, 3GCR: 27-72%
K. pneumoniae, CR: 0-8%
P. aeruginosa, MDR: 30-35%
A. baumannii, CR: 62-72%
S. aureus, MR: 4-84%
Region of the Americas
European Region
Eastern Mediterranean Region
African Region
South-East Asia
Western Pacific Region


Imported MDRB
ASP
In-ICU broad-spectrum antimicrobial exposure
ASP
Commensal ecosystems
Site of infection
Colonization pressure
Altered resistance to colonization with MDRB
« Direct » selection pressure
ICP
Cross-transmission of MDRB
In situ selection of MDRB
ICU-acquired MDRB
Burden of MDRB in the ICU


Infection site
Most probable pathogens
Risk factors for MDR pathogens
Molecular microbiology results
Clinical severity
Dose optimisation
Best practice for empirical antibiotic treatment in critically ill patients

Patient factors

- Age
- nutritional status
- Site of infection
- Other co morbid condition like diabetes

Predictors of MDRB infection	At ICU admission	During the ICU stay
Patient features	Co-morbid illness/immunosuppression/recent hospital and/or ICU stay	Higher severity of acute illness/Invasive interventions
Type of infection	Hospital-acquired > healthcare-associated > community-acquired	ICU-acquired > others
Antimicrobial selection pressure	Prior antibiotics*/antifungals	Antibiotics*/antifungals in the ICU
Colonization status	Previously documented colonization with MDRB	In-ICU acquisition of MDRB
Local epidemiology	Epidemiology of MDRB in community/hospital/areas recently traveled to	Local epidemiology of MDRB in the ICU
Infection prevention measures	Poor hygiene practices in hospital	Poor hygiene practices in the ICU

MDRB multidrug-resistant bacteria, *ICU* intensive care unit

*Especially if agents with broad-spectrum and/or potent activity against intestinal anaerobes

	Suggested microbiological sampling	Examples of source control	Peculiarities	Notes on antibiotics penetration⁎
Lungs	Bronchoalveolar lavage, protected specimen brushing, or endotracheal aspirate; blood cultures	Drainage of pleural empyema	The epithelial lining fluid is the main site to reach. Diffusion of antibiotics is hampered by the alveolar–blood barrier, as the alveolar wall has no fenestration	β-lactams have good penetration, but higher doses c considered to increase it. Consider fluoroquinolones. Linezolid has good penetration. Colistin and aminoglycosides have poor penetration; nebulisation be considered
Urinary tract	Urinary cultures; blood cultures	Removal of urinary catheter, nephrostomy	Good penetration for antimicrobials with urinary excretion	Consider β-lactams, aminoglycosides, fluoroquinolor achieve good concentrations
Abdomen	Percutaneous drainage or open surgical sampling during source control; blood cultures	Drainages, debridement, or both	Enterobacterales, enterococci or *Candida* spp. are commonly involved	Consider β-lactams, aminoglycosides, fluoroquinolor tigecycline have good penetration
Central nervous system	CSF sample; blood cultures	Removal of invasive devices; surgical decompression	Penetration dependent on integrity of blood–brain barrier and inflammation of meningitis (e.g. reduced in case of acidosis)	Consider β-lactams and rifampicin have good penetr Consider aminoglycosides with intrathecal administr Vancomycin i.v. or intrathecal is an option. Meropene dose is commonly used in the UK. Colistin has poor penetration, intrathecal administrat be considered
Soft tissues and bones	Surgical sampling; blood cultures	Surgical debridement	Despite rigid structure of bones and low vascularisation of soft tissue, most antibiotics have good penetration	Consider clindamycin, β-lactams, daptomycin and linezolid have good penetration
Bloodstream	Blood cultures	Removal of venous catheters	Easy to reach. Effect site concentration is equal to plasma concentration	As it is easy to achieve good concentrations, choice be based on minimum inhibitory concentration of the microorganisms, alteration of patient's body fluids compartments (i.e. septic shock)

Risk Factors for MDR

MDR Gram-negative	Local epidemiology; invasive procedures (e.g. abdominal surgery)
	Presence of a prior gastrointestinal colonisation status or recent infection caused by MDR pathogens
	Broad-spectrum antibiotics use during the preceding 90 days
	Prolonged mechanical ventilation (≥48 h) or ICU stay
	Recent hospitalisation for at least 5 days in the past 90 days
	Immunosuppression
MRSA[4]	Local epidemiology, history of MRSA infection or colonisation
	Recent i.v. antibiotics
	Recurrent skin infections or chronic wounds
	Invasive devices
	Haemodialysis

Bug Factors

Classes	Resistance	Examples of treatment options*
Class A, extended-spectrum β-lactamases (ESBLs)	Resistant to third generation or higher cephalosporins (e.g. ceftriaxone)	Carbapenems
Class A, serine carbapenemases (KPC)	Resistant to β-lactams including carbapenems	Meropenem–vaborbactam; ceftazidime–avibactam; fosfomycin; colistin
Class B, metallo-β-lactamases (NDM, VIM, IMP1)	Resistant to all β-lactams except for aztreonam. Note that they are usually also producing ESBL (resistance to aztreonam)	Ceftazidime–avibactam + aztreonam; meropenem–vaborbactam + aztreonam; cefiderocol; colistin + fosfomycin
Class C, AmpC β-lactamase	Resistant to cephalosporins	Carbapenems, ceftolozane–tazobactam
Class D, oxacillinases (OXA-23, OXA-48, OXA-48-like etc.)	Frequently combined with ESBL and AmpC. Resistance against cephalosporins and carbapenems and vaborbactam or relebactam	Ceftazidime–avibactam; cefiderocol; fosfomycin; colistin

Methicillin-resistant *Staphylococcus aureus*	Resistant to β-lactams. Some species may be also vancomycin-resistant (VRSA)	Vancomycin; linezolid; daptomycin; ceftaroline; telavancin; ceftobiprole
Pseudomonas aeruginosa	Rifampin, tetracycline, chloramphenicol, trimethoprim–sulfamethoxazole; frequently resistant to fluoroquinolones and many β-lactams, including carbapenems	Piperacillin–tazobactam; levofloxacin; cefepime; ceftazidime. In difficult-to-treat cases: ceftolozane–tazobactam, ceftazidime–avibactam or imipenem–cilastatin–relebactam (when not susceptible to carbapenems and traditional β-lactams); cefiderocol in case of metallo-β-lactamases producing strain
Acinetobacter baumannii	Glycopeptides, lincosamides, macrolides, streptogramins; frequently resistant to all β-lactam including carbapenems	Combination therapy with at least two active agents for severe infections; polymyxin (e.g. colistin) + ampicillin/sulbactam; cefiderocol (in combination if possible); inhaled colistin may be considered for HAP/VAP caused by CRAB

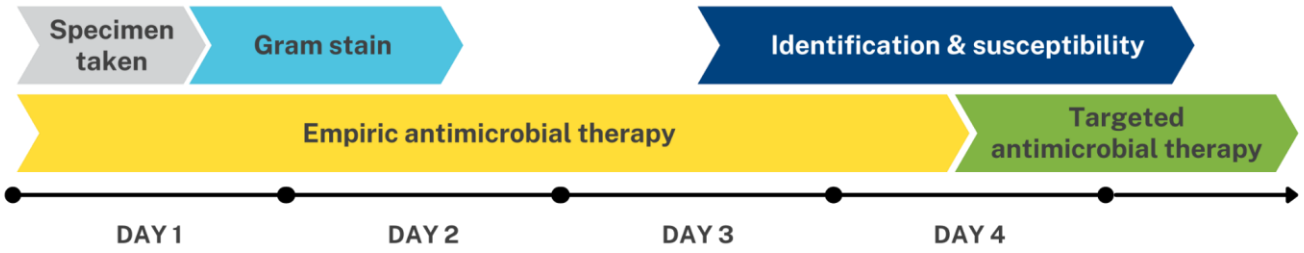
Method	Based on	Available	Pros	Cons
Direct AST	Culture	Yes	Cheap Decreases TAT by 24 h	Lacks standardization Does not work for polymicrobial infection
Accelerate Pheno™	Culture	Yes	Faster than conventional methods Automatized 1 h for identification, 6–8 h for AST	Expensive Low throughput For positive blood cultures only
Lab automation	Culture	Yes	Real-time culturing decreasing TAT	Integration with stewardship Cost Exploitation of results outside working hours
Syndromic tests	PCR	Yes	Fast (TAT 1–8 h) Minimal hands-on time	Expensive Not exhaustive Minimal information on antibiotic resistance
Clinical metagenomics	NGS	In development	Exhaustive Potentially fast Host response	Experimental Interpretation of results Expensive

AST antimicrobial susceptibility testing, *TAT* turnaround time, *NGS* next-generation sequencing

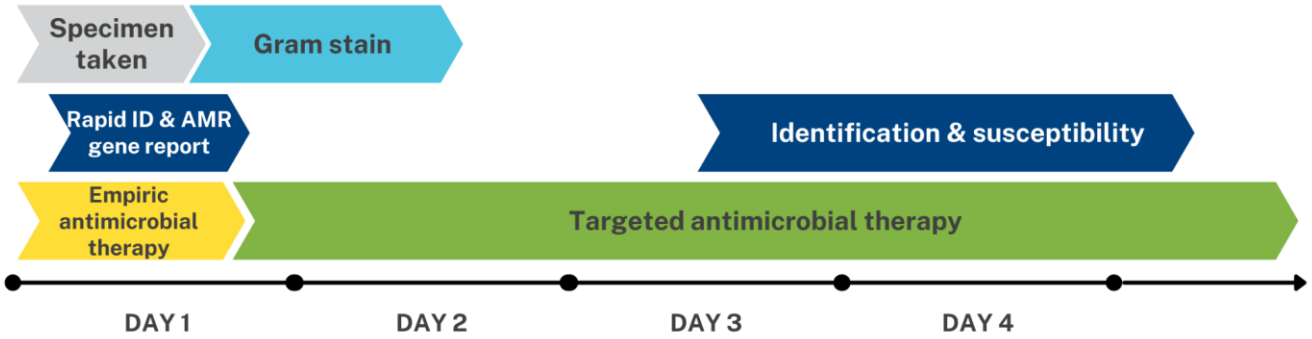
THE SYNDROMIC APPROACH

Conventional vs syndromic testing

Conventional ID/AST



Syndromic Testing



WHY USE SYNDROMIC APPROACH?

- To detect relevant pathogens involved in the disease
- To detect unsuspected pathogen(s)
- To detect additional under diagnosed pathogens
- To detect co-infections
- To help clinicians in their clinical decisions about Patient management
- To generate savings at the patient and hospital level

The BIOFIRE® FilmArray® System

All-in-one integration of

Sample preparation

Amplification

Detection

BIOFIRE®

RESPIRATORY 2.1 *PLUS* (RP2.1*plus*) PANEL

1 Test. 23 Targets. ~45 Minutes.

VIRUSES

- Adenovirus
- Coronavirus 229E
- Coronavirus HKU1
- Coronavirus NL63
- Coronavirus OC43
- Middle East respiratory syndrome coronavirus (MERS-CoV)
- Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
- Human metapneumovirus
- Human rhinovirus/enterovirus
- Influenza A virus
- Influenza A virus A/H1
- Influenza A virus A/H3
- Influenza A virus A/H1-2009
- Influenza B virus
- Parainfluenza virus 1
- Parainfluenza virus 2
- Parainfluenza virus 3
- Parainfluenza virus 4
- Respiratory syncytial virus

BACTERIA

- *Bordetella parapertussis*
- *Bordetella pertussis*
- *Chlamydia pneumoniae*
- *Mycoplasma pneumoniae*

CE 2797

Overall Performance: 97.1% sensitivity, 99.3% specificity[1]
SAR-CoV-2 Performance: 98.4% PPA, 98.9% NPA[2]

Sample Type: 0.3mL of nasopharyngeal swab in transport media or saline

1. Overall performance based on prospective clinical study for the BIOFIRE® FILMARRAY® Respiratory 2 *plus* Panel, Data on file, BIOFIRE Diagnostics.
2. Overall performance based on prospective SARS-CoV-2 clinical study for the BIOFIRE® Respiratory 2.1 *plus* Panel in comparison to 3 EUA tests, Data on file, BIOFIRE Diagnostics.

Traditional diagnostic methods

Traditional diagnostic methods are technically cumbersome, require highly skilled labour, have long turnaround time (TAT), detect a limited range of pathogens, and/or have poor diagnostic performance

Bacterial culture[1–7]

- Poor sensitivity, particularly for fastidious organisms and in patients who have received prior antimicrobials
- Potential contamination with normal oropharyngeal flora
- Labour-intensive; results interpretation can be subjective
- Long TAT
- Requires specialised facilities and/or reagents

AST[8–11]

- Variable performance of different AST methods
- Labour-intensive; requires interpretation by trained personnel
- Long TAT
- Limited use in the detection of fastidious and/or atypical organisms

Pneumococcal and *Legionella* UAT[12–14]

- Poor sensitivity
- Increased risk of clinical relapse from inappropriate therapy de-escalation (pneumococcal UAT)
- Limited coverage for *L. pneumophila* serotype 1 (*Legionella* UAT)

NAATs for viruses/atypical bacteria[15,16]

- Labour-intensive
- Requires multiple tests for detection of multiple pathogens (singleplex assays)
- May require samples to be sent to specialised laboratory facilities
- Requires use in conjunction with bacterial culture to avoid over- and/or under-treatment

AST: antimicrobial susceptibility testing; NAAT: nucleic acid amplification test; TAT: turnaround time; UAT: urinary antigen testing.

[1]Poole, et al. J Infect 2020;80(1):1-7; [2]Boruchoff, et al 2021. Available here; [3]Murdoch, et al 2022. Available here; [4]Baum S 2020. Available here; [5]Lagier, et al. Clin Microbiol Rev 2015;28(1):208-36; [6]Campbell, et al. J Clin Microbiol 2011;49(9 Suppl):S30-3; [7]Hashimoto, et al. J Intensive Care 2013;1(1):2; [8]Lee, et al. J Microbiol Methods 2015;112:87-91; [9]Bard, et al. Clin Microbiol Newsl 2018;40(11):87-95; [10]van Belkum, et al. Nat Rev Microbiol 2019:17(1)51-62; [11]Turbett, et al 2019. Available here; [12]Murdoch, et al 2020. Available here; [13]Hyams, et al. ERJ Open Res 2020;6(1):00223-2019; [14]Metlay, et al. Am J Respir Crit Care Med 2019:200(7):e45-67; [15]Crowe JE 2021. Available here; [16]Klompas M 2021. Available here.