Integration of Molecular Diagnostics into Stewardship Practices

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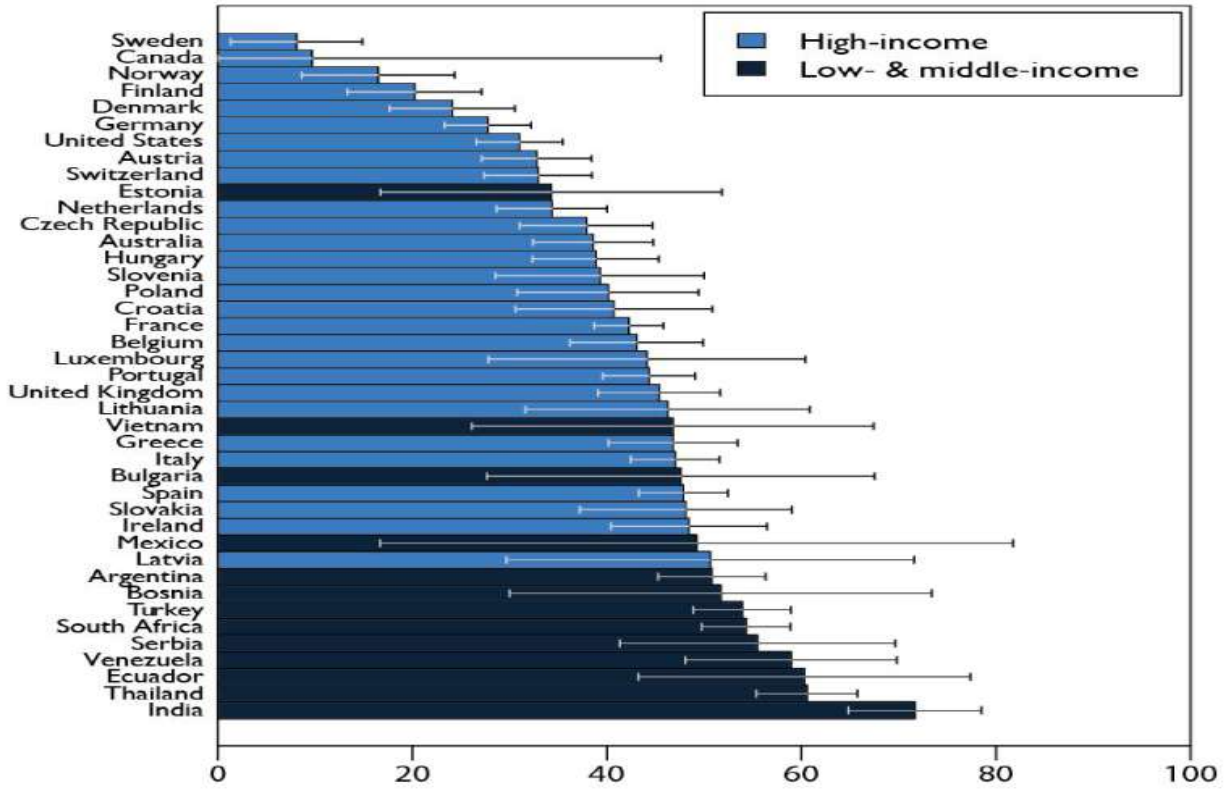
Global burden

- The global burden associated with drug-resistant infections assessed across 88 pathogen–drug combinations in 2019 was an estimated 4·95 million (95% UI 3·62–6·57) deaths, of which 1·27 million (0·911–1·71) deaths were directly attributable to drug resistance.
- Analysis showed that AMR all-age death rates were highest in some LMICs, making AMR not only a major health problem globally but a particularly serious problem for some of the poorest countries in the world.
- By any metric, bacterial AMR is a leading global health issue.

Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. January 20, 2022 https://doi.org/10.1016/ S0140-6736(21)02724-0. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)02724-0/fulltext. Last accessed Feb. 6, 2022.

Drug Resistance Index across countries



The State of the World's Antibiotics 2021. A Global Analysis of Antimicrobial Resistance and Its Drivers.
© The Center for Disease Dynamics, Economics & Policy (CDDEP), Inc. 2021. Last accessed Feb. 6, 2020.

Global deaths (counts) attributable to and associated with bacterial antimicrobial resistance by pathogen

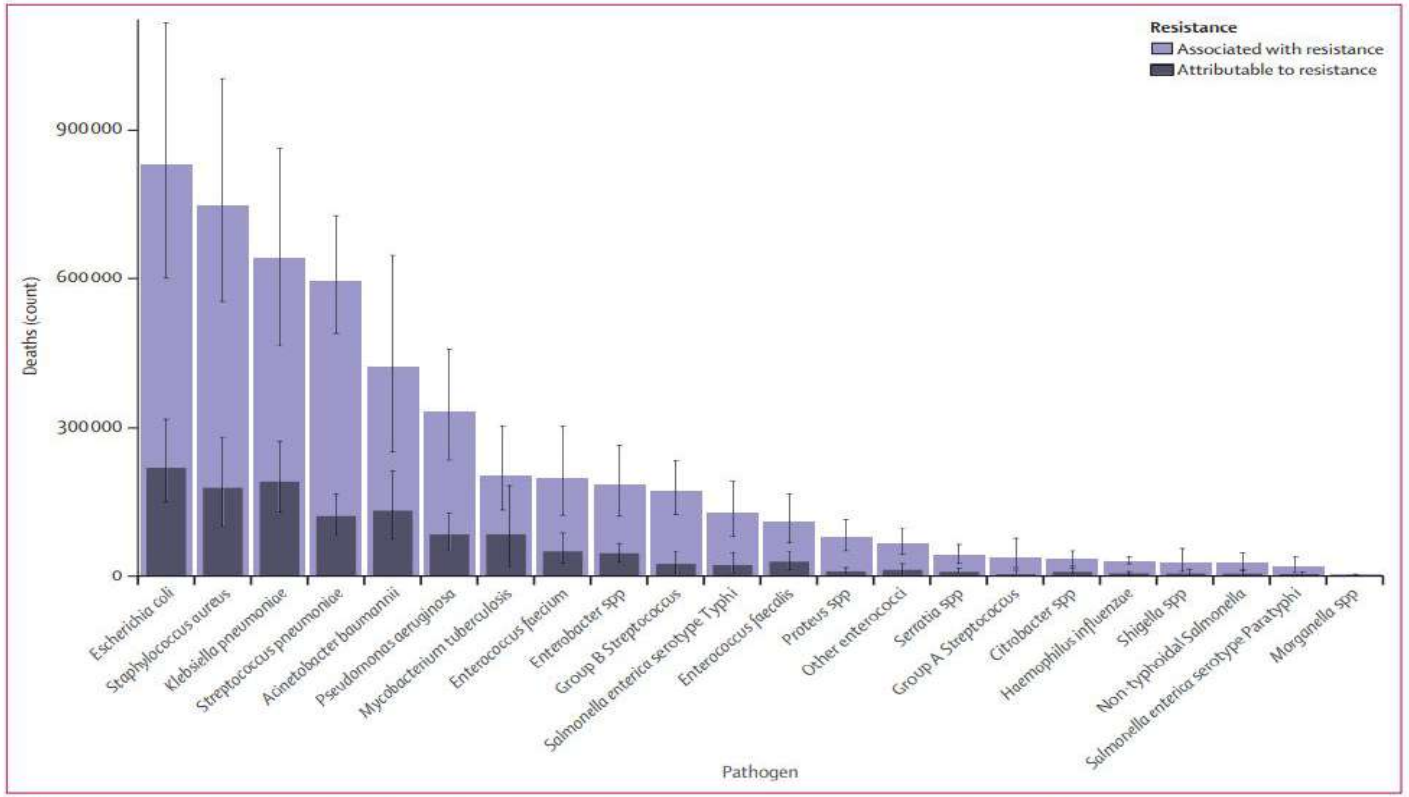
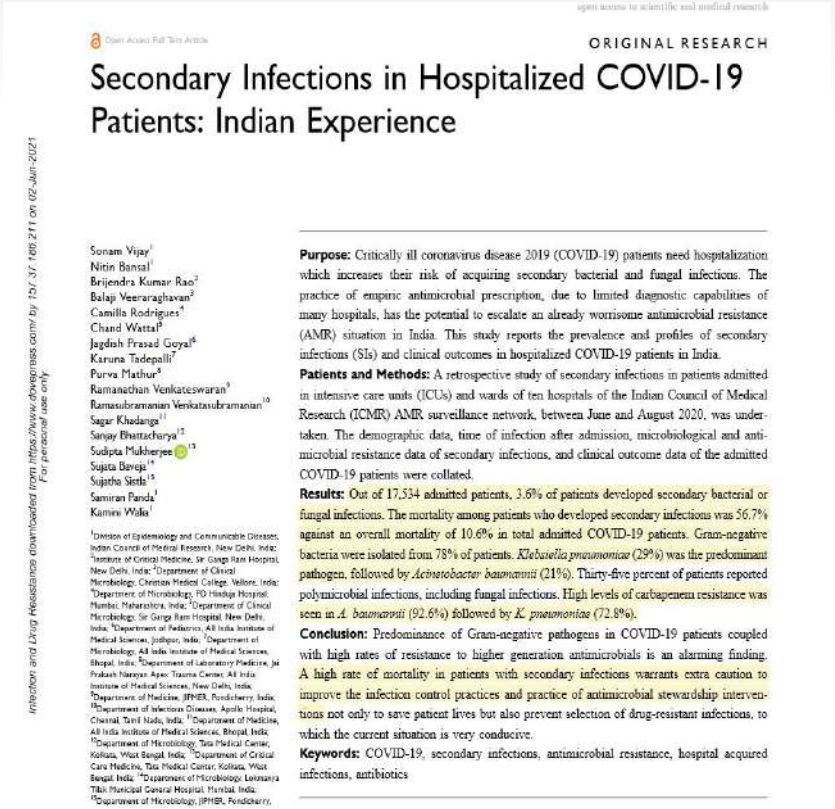


Figure 4: **Global deaths (counts) attributable to and associated with bacterial antimicrobial resistance by pathogen, 2019**
Estimates were aggregated across drugs, accounting for the co-occurrence of resistance to multiple drugs. Error bars show 95% uncertainty intervals.

Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. January 20, 2022 https://doi.org/10.1016/ S0140-6736(21)02724-0. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)02724-0/fulltext. Last accessed Feb. 6, 2022.

Secondary Infections in Hospitalized COVID patients: *Indian Experience*



ORIGINAL RESEARCH

Secondary Infections in Hospitalized COVID-19 Patients: Indian Experience

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Purpose: Critically ill coronavirus disease 2019 (COVID-19) patients need hospitalization which increases their risk of acquiring secondary bacterial and fungal infections. The practice of empiric antimicrobial prescription, due to limited diagnostic capabilities of many hospitals, has the potential to escalate an already worrisome antimicrobial resistance (AMR) situation in India. This study reports the prevalence and profiles of secondary infections (SIs) and clinical outcomes in hospitalized COVID-19 patients in India.

Patients and Methods: A retrospective study of secondary infections in patients admitted in intensive care units (ICUs) and wards of ten hospitals of the Indian Council of Medical Research (ICMR) AMR surveillance network, between June and August 2020, was undertaken. The demographic data, time of infection after admission, microbiological and antimicrobial resistance data of secondary infections, and clinical outcome data of the admitted COVID-19 patients were collated.

Results: Out of 17,534 admitted patients, 3.6% of patients developed secondary bacterial or fungal infections. The mortality among patients who developed secondary infections was 56.7% against an overall mortality of 10.6% in total admitted COVID-19 patients. Gram-negative bacteria were isolated from 78% of patients. *Klebsiella pneumoniae* (29%) was the predominant pathogen, followed by *Acinetobacter baumannii* (21%). Thirty-five percent of patients reported polymicrobial infections, including fungal infections. High levels of carbapenem resistance was seen in *A. baumannii* (92.6%) followed by *K. pneumoniae* (72.8%).

Conclusion: Predominance of Gram-negative pathogens in COVID-19 patients coupled with high rates of resistance to higher generation antimicrobials is an alarming finding. A high rate of mortality in patients with secondary infections warrants extra caution to improve the infection control practices and practice of antimicrobial stewardship interventions not only to save patient lives but also prevent selection of drug-resistant infections, to which the current situation is very conducive.

Keywords: COVID-19, secondary infections, antimicrobial resistance, hospital acquired infections, antibiotics

A 2020 study of over 17,000 hospitalized COVID patients revealed:

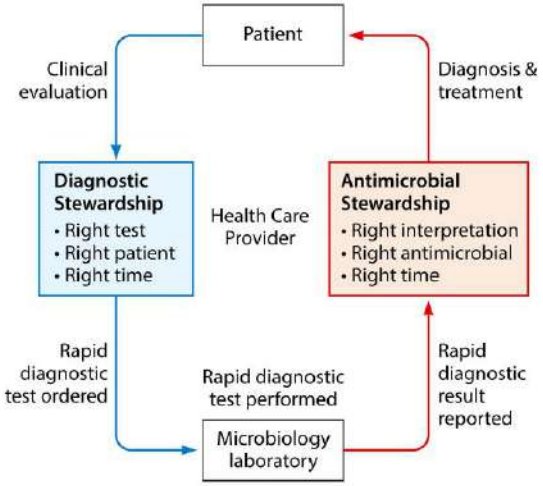
- **78%** patients acquiring secondary infections harbored GNB.
- **74.2%** of GNBs were carbapenem resistant.
- **72.8%** of *Klebsiella pneumoniae* and **92.6%** of *Acinetobacter baumannii* isolates respectively were carbapenem resistant.
- **72%** of deaths due to secondary infections were attributable to GNBs.
- **75%** of patients acquired a secondary infection within 48 hours of hospitalization, making hospital-acquired infections (HAIs) the likely cause of secondary infections.
- **2–3 fold** increased bloodstream infection (BSI) rates in most hospitals.

Vijay et al Infection and Drug Resistance May 2021:14 1893–1903. Last accessed Feb.6, 2022.

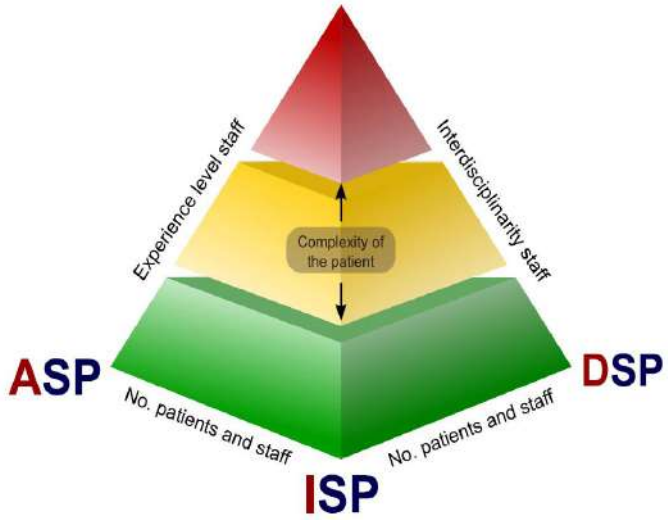
Urgent need to reinforce infection control and antibiotic stewardship.

•. 2017 Nov;55(11):3306-330

Interactions between antimicrobial stewardship, diagnostic stewardship and infection prevention



- Critical importance of integrating rapid diagnostics not only with individual patient management but with infection prevention modalities such as ensuring minimal unnecessary time spent in isolation, best use of scant infection prevention resources



Dik et al, J Clin Micro 2017, 55: 3306-3307

Key questions that rapid molecular diagnostics could address:

- ❑ Is the patient infected/colonized?
- ❑ Bacterial or viral?
- ❑ Pathogen diagnosis for a clinical syndrome – meningitis, respiratory tract infection, sexually transmitted infection
- ❑ Direct detection of pathogens from blood or positive blood culture
- ❑ Rapid antibiotic susceptibility testing
- ❑ Rapid detection of resistance mechanisms

Does the patient have infection/sepsis?

Some options :

- ❑Transcriptomics – targeted host immune gene expression (mRNA) profiling for diagnosis
- ❑Transcriptomics in risk profiling

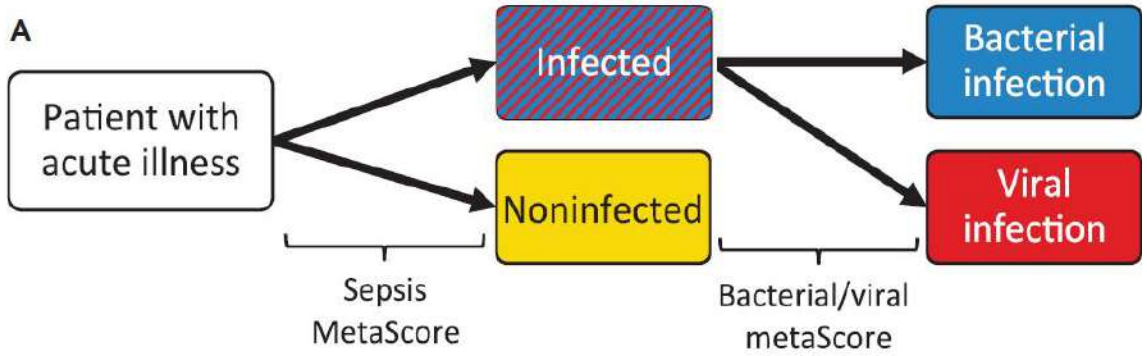
Robust classification of bacterial and viral infections via integrated host gene expression diagnostics

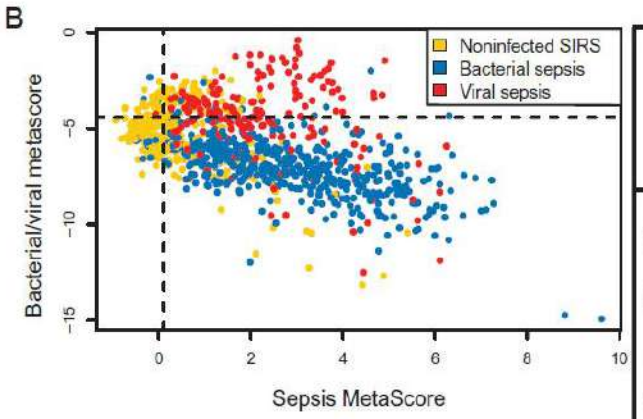
Timothy E. Sweeney,[1,2]* Hector R. Wong,[3,4] Purvesh Khatri[1,2]*

Study describes the use of a eleven-gene sepsis meta-score together with a seven-gene bacterial/viral score to build an integrated antibiotic decision model

Sensitivity and specificity for bacterial infections in this study was 94% and 59.8% respectively

Prospective clinical validation required before this could be used in the clinic –some of these now being reported





C

Ground truth	Predicted: Noninfected	Predicted: Bacterial	Predicted: Viral
Noninfected	137	115	67
Bacterial	19	504	13
Viral	1	94	107

Sci Transl Med, 2016:8;346 -

The Effect of Molecular Rapid Diagnostic Testing on Clinical Outcomes in Bloodstream Infections: A Systematic Review and Meta-analysis

- Meta-analysis of 31 studies with 5920 patients
- Mortality risk significantly lower with molecular rapid diagnostic testing compared to conventional microbiology methods, with number needed to treat of 20
- Mortality lower in studies with antimicrobial stewardship programmes
- Time to therapy and length of stay both decreased

Timbrook et al Clin Infect Dis 2017 Jan 1;64(1):15-23

Syndromic approach

Dr. Debkishore Gupta

Infectious Syndromic Testing

The **syndromic** approach represents a new line of diagnosis against infectious diseases by using a single rapid, **test** for the most microorganisms responsible for an infectious disease.

Present Challenges

- The current standard-of-care, which depends on culture-based initial diagnosis, often takes at least 48–72 hours to provide a result.
- Cultures can remain negative even when bacterial or fungal infections are strongly suspected.
- Viruses and parasites are often detected by indirect means.
- Ineffective antimicrobial therapy increases mortality rate.
- Use of unnecessary empiric antimicrobial agents increases AMR.

Possible reasons PCR detects organisms that culture can not:

- Fastidious organisms
- Antibiotic treatment prior to sample collection
- Variability in normal oral flora definitions and reporting
- Sample transport conditions
- Patient immune factors

Solutions at hand

- Easy – Few minutes hands-on time
- Fast – Results in minutes to about 1 hour
- Comprehensive Panels:
  - -Respiratory Panel: Xpert® Xpress CoV-2/Flu/RSV plus and Biofire FilmArray
  - -Blood Culture Panel: Biofire FilmArray
  - -Gastrointestinal Panel: Biofire FilmArray
  - -Meningitis / Encephalitis Panel: Biofire FilmArray
  - -Sexual health: Xpert® CT/NG
- Contamination Free Closed System
- Small footprint
- No molecular skills needed
- No sophisticated setup required

- Can detection of resistance mechanisms assist with antimicrobial stewardship in addition to impacting infection prevention?

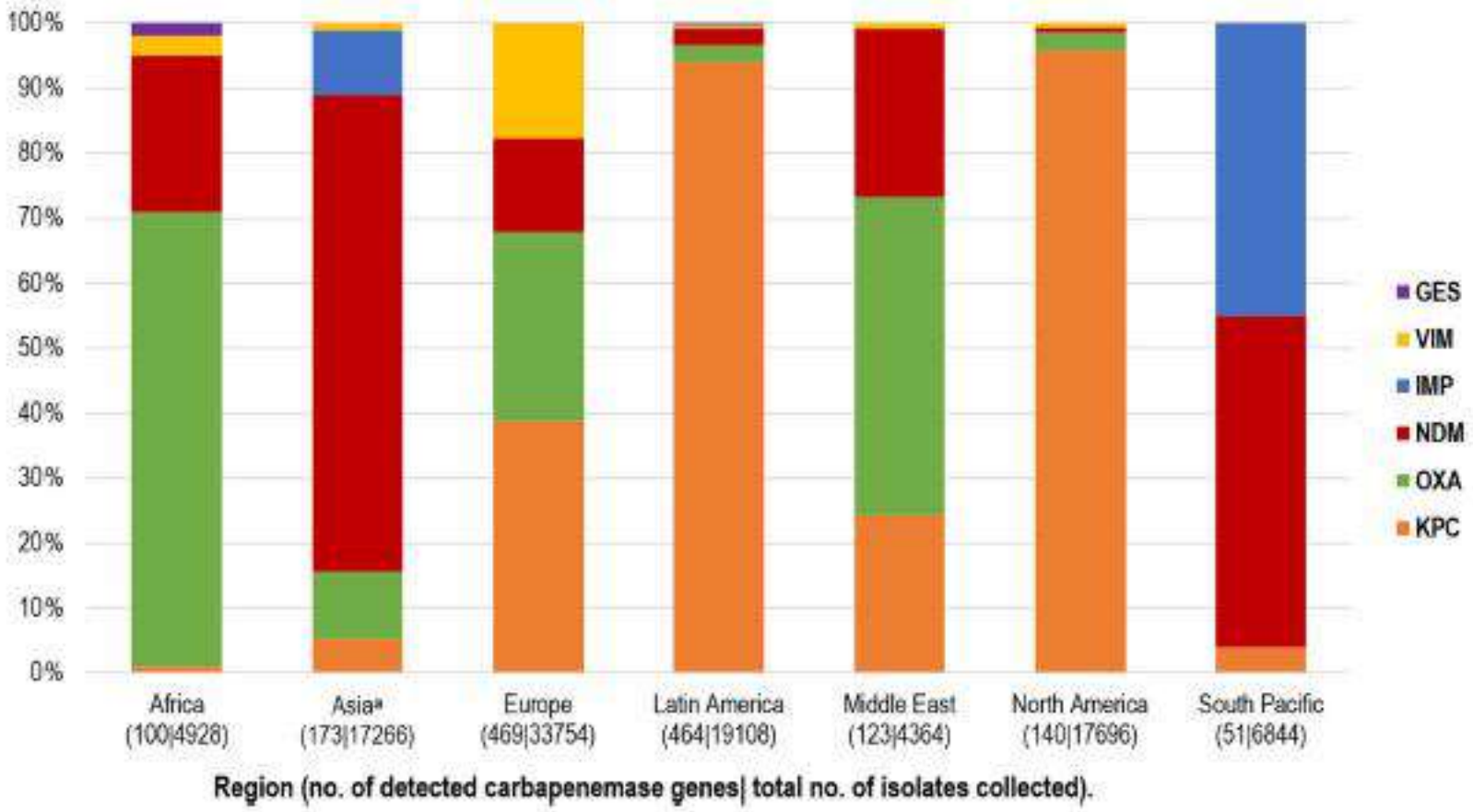
TABLE 1 | Classification and characteristics of major carbapenemases in *Enterobacteriaceae*.

Carbapenemase	KPC	MBLs (NDM, VIM, IMP)	OXA-48
Ambler molecular class	A	B	D
Substrates of hydrolysis	All β-lactams	All β-lactams except for aztreonam	Penicillins and carbapenems
Inhibited by classic β-lactamase inhibitors	Minimally	No	No
Inhibited by avibactam	Yes	No	Yes
Inhibited by vaborbactam	Yes	No	No
Inhibited by relebactam	Yes	No	No
Common species in *Enterobacteriaceae*	*K. pneumoniae, E. coli, Enterobacter* spp.	NDM: *K. pneumoniae, E. coli* VIM: *K. pneumoniae* IMP: *K. pneumoniae*	*K. pneumoniae*

KPC, Klebsiella pneumoniae carbapenemase; MBL, metallo-β-lactamase; NDM, New Delhi metallo-β-lactamase; VIM, Verona integrin-encoded metallo-β-lactamase; IMP, imipenemase; OXA, oxacillinase.

Sheu et al Front Microbiol 2019. Last accessed Feb.6, 2022

Relative Percentages of Carbapenemase Types Detected by Global Regions



Karlowsky et al, JCM 2017. Last accessed Feb.6, 2022.

Clinical Features & Outcomes of BSI Caused by NDM-1

- Blood isolates from 40 patients with NDM bacteremia were studied.
- Half of the bacteremic patients were cared for in medical wards, and 47.5% had malignancy.
- The majority of patients (67.5%) had previous documented rectal NDM colonization.
- *The predominant organism was Klebsiella pneumoniae.*
- The overall 30-day mortality rate was 42.5%.
- Septic shock occurred in 32.5% of patients.

Falcone et al. Clinical Features and Outcomes of Bloodstream Infections Caused by New Delhi Metallo-β-Lactamase–Producing Enterobacterales During a Regional Outbreak. Open Forum Infectious Diseases, Volume 7, Issue 2, February 2020, ofaa011, https://doi.org/10.1093/ofid/ofaa011. Last accessed Feb.6, 2022.

CPE Screening

Dr. Debkishore Gupta

Risk of infection following colonization with carbapenem-resistant Enterobactericeae: A systematic review

Jessica Tischendorf MD [a], Rafael Almeida de Avila [b], Nasia Safdar MD, PhD [a,c,*]

Characteristics of studies included in the review

Study, year	Patient population	Outbreak setting	Screening frequency	No. of patients colonized by CRE	No. of patients who developed CRE infection
Borer et al, 2012[12]	Adults, hospital-wide	No	Rectal cultures performed in patients admitted for nursing or other outside facility and on patients in high-risk units	464	42 (9.1%)
Cho et al, 2014[13]	Adults, ICU	No	On admission, weekly thereafter	530 with nosocomial acquisition included for analysis	111 (20.9%)
Debby et al, 2012[14]	Adults, ICU	No	Within 72 h of ICU admission, then twice weekly	48 with nosocomial acquisition included for analysis	20 (41.7%)
Wiener-Well et al, 2010[15]	Adults, hospital-wide	Yes	All hospitalized patients screened during 3 consecutive days	42, 16 with CRKP included for analysis	5 (31.3%)
Papadimitriou-Olivgeris et al, 2013[16]	Adults, ICU	No	Upon ICU admission, days 4 and 7, and weekly thereafter	164	37 (22.6%)
Lübbert et al, 2014[17]	Liver transplant patients	Yes	—	9	8 (89%)
Pisney et al, 2014[18]	Adults, selected high-prevalence units	Yes	7 rounds of point prevalence screening on affected units	15	0 (0.0%)
Lowe et al, 2013[19]	Adults, hospital-wide	No	Known contact with CRE-infected patients were screened	9	4 (44.4%)
Schechner et al, 2012[20]	Adults, hospital-wide	Yes	All patients hospitalized in the past year and those with CRE-infected contact	502	38 (7.6%)
Latibeaudire, et al, 2015[11]	Adults, ICU	No	Upon ICU admission and weekly thereafter	49	34 (69%)

Tischendorf et al, AJIC 2016. Last accessed Feb.6, 2022

Implementation manual to prevent and control the spread of carbapenem-resistant organisms at the national and health care facility level

Interim practical manual supporting implementation of the Guidelines for the prevention and control of carbapenem-resistant Enterobacteriaceae, *Acinetobacter baumannii* and *Pseudomonas aeruginosa* in health care facilities

World Health Organization

Potential barriers and solutions

- Lack of AMS in place in a tertiary care facility in LICs.
- Limited microbiology laboratory capacity including staff.
- Inability to effectively use data due to lack of expertise in data interpretation and lack of reporting mechanisms and effective feedback.
- Defective communication.
- Lack of engagement by senior managers/leaders, resulting in low financial support.

Implementation manual to prevent and control the spread of carbapenem-resistant organisms at the national and health care facility level: interim practical manual supporting implementation of the Guidelines for the prevention and control of carbapenem-resistant Enterobacteriaceae, Acinetobacter baumannii and Pseudomonas aeruginosa in health care facilities. WHO. Document no. WHO/UHC/SDS/2019.6. https://apps.who.int/iris/handle/10665/312226. Last accessed Feb.6, 2022.

Enhancing the usefulness of surveillance and screening

- Adequate resources to support implementation
- Clear definition of the objectives
- Appropriate sample collection approach: timeliness, clear roles and responsibilities indicating who should collect the samples, including the appropriate technique
- Reliable microbiological methods for microorganism identification and resistance detection
- Rapid return of results
- Clear actions depending on the results

Implementation manual to prevent and control the spread of carbapenem-resistant organisms at the national and health care facility level: interim practical manual supporting implementation of the Guidelines for the prevention and control of carbapenem-resistant Enterobacteriaceae, Acinetobacter baumannii and Pseudomonas aeruginosa in health care facilities. WHO. Document no. WHO/UHC/SDS/2019.6. https://apps.who.int/iris/handle/10665/312226. Last accessed Feb.6, 2022.

Selection of test depends upon:

- **Local carbapenemase prevalence**
- Regional molecular epidemiology
- Diagnostic performance characteristics
- Labor intensity
- Cost
- **Turnaround time (TAT)**
- Organisms to be tested (i.e., *Enterobacterales* and/or glucose-nonfermenting Gram negatives)
- **Ease of use**
- Workflow
- Necessary equipment
- Reagent preparation requirements
- Regulatory status

Implementation manual to prevent and control the spread of carbapenem-resistant organisms at the national and health care facility level: interim practical manual supporting implementation of the Guidelines for the prevention and control of carbapenem-resistant Enterobacteriaceae, Acinetobacter baumannii and Pseudomonas aeruginosa in health care facilities. WHO. Document no. WHO/UHC/SDS/2019.6. https://apps.who.int/iris/handle/10665/312226. Last accessed Feb.6, 2022.

Reluctance to using Molecular Diagnostic Tests For CPO Detection

- There is a sense that differentiation by carbapenem resistance genes is simply unnecessary
- Laboratories tend to assume that any gram negative Enterobacteriaceae isolate that tests as resistant to any carbapenem is a carbapenemase producer (CPE)
- Another source of reluctance is the presumption that carbapenem resistance in isolates of *Pseudomonas aeruginosa* and *Acinetobacter species* is not mediated by CRG
- Reluctance also comes from the confusion over which tests have received regulatory approval for developing therapeutic strategies for infections versus tests approved only to guide infection control interventions

Tenover et al. Using Molecular Diagnostics to Develop Therapeutic Strategies for Carbapenem-Resistant Gram-Negative Infections. *Front. Cell. Infect. Microbiol.*, 28 September 2021 | https://doi.org/10.3389/fcimb.2021.715821. https://www.frontiersin.org/articles/10.3389/fcimb.2021.715821/full. Last accessed Feb.6, 2022.

Why would we need molecular detection?

- Fast availability of results – aids patient management and infection prevention actions
- Higher sensitivity and specificity compared over conventional phenotypic tests
- Possibility of detecting enzyme co-expression by molecular platforms
- Information regarding mechanism of resistance may aid in outbreak management
- Local, national and global surveillance of AMR

Screening for carbapenemase production (EUCAST)- Phenotypical

Enterobacterales *

Expert Rules and Intrinsic Resistance Tables

EUCAST Clinical Breakpoint Tables v. 11.0, valid from 2021-01-01

Carbapenems[1]	MIC breakpoints (mg/L)			Disk content (µg)	Zone diameter breakpoints (mm)			Notes
	S ≤	R >	ATU		S ≥	R <	ATU	Numbered notes relate to general comments and/or MIC breakpoints. Lettered notes relate to the disk diffusion method.
Doripenem	1	2		**10**	24	21		**1.** Some isolates that produce carbapenemase are categorised as susceptible with the current breakpoints and should be reported as tested, i.e. the presence or absence of a carbapenemase does not in itself influence the categorisation of susceptibility. Carbapenemase detection and characterisation are recommended for public health and infection control purposes. For carbapenemase screening a meropenem screening cut-off of >0.125 mg/L (zone diameter <28 mm) is recommended. **2.** The intrinsically low activity of imipenem against *Morganella morganii*, *Proteus* spp. and *Providencia* spp. requires the high exposure of imipenem. **3.** For susceptibility testing purposes, the concentration of relebactam is fixed at 4 mg/L. **4.** For susceptibility testing purposes, the concentration of vaborbactam is fixed at 8 mg/L.
Ertapenem	0.5	0.5		**10**	25	25		
Imipenem, *Enterobacterales* except *Morganellaceae*	2	4		**10**	22	19		
Imipenem[2], *Morganellaceae*	0.001	4		**10**	50	19		
Imipenem-relebactam, *Enterobacterales* except *Morganellaceae*	2[3]	2[3]		**10-25**	22	22		
Meropenem (indications other than meningitis)	2	8		**10**	22	16		
Meropenem (meningitis)	2	2		**10**	22	22		
Meropenem-vaborbactam	8[4]	8[4]		**IP**	IP	IP		

Carbapenemase-positive Enterobacteriaceae: Global MIC Distributions

Karlowsky et al, JCM 2017

- Not all carbapenemase-producing bacteria are detected by phenotypic tests; some have MICs in the susceptible range
- These would be unrecognized unless all bacteria are tested with a specific test for carbapenemases

Isolate Genotype (no.)	Percent of Isolates with Imipenem MIC		
	0.12 – 1 (Susc)	2 (Intermediate)	≥4 (Resistance)
KPC (794) (Class A)	2.3	8.3	89.4
NDM (290) (Class B)	0	0.7	99.3
VIM (92) (Class B)	3.3	14.1	82.6
IMP (40) (Class B)	20.0	47.5	32.5
OXA-48-like (300) (Class D)	37.0	35.3	27.7

EUCAST. 2015. EUCAST breakpoint tables for interpretation of MICs and zone diameters. Version 5.0, January. http://www.eucast.org/clinical _breakpoints/.

Culture based versus molecular detection of CPEs?

- **Culture based:**
  - Relies on selective media
  - Can be insensitive especially for some CPEs
  - Turnaround time slow – complex to confirm after preliminary culture
  - Culture available for further testing

- **Molecular:**
  - Sensitive and specific
  - Turnaround time can be fast depending on system used
  - Require continual updating to detect new CPEs
  - Acquisition costs higher – but what about impact?

Table 1: Nucleic acid and non-nucleic acid-based assays as point of care testing for detection of carbapenem resistance in Gram-negative organisms

Assay	Method	Turnaround time	Source	Detection of carbapenemases gene	Sensitivity (%)	Specificity (%)	Approval	References
Nucleic acid-based detection								
Entericbio CPE assay	Real-time multiplex PCR	2 h	Culture, swabs	KPC, IMP, VIM, NDM, Oxa48-like, GES-5, IMI, OXA-23	100	100		[63]
Xpert Carba-R	Real-time multiplex PCR	2 h	Culture	KPC, IMP, VIM, NDM, Oxa48-like	100	100	CE-IVD FDA IVD	[64]
Check-Direct CPE assay	Real-time multiplex PCR	3.5 h	Rectal swab/ culture	KPC, OXA-48 including OXA-181, VIM and NDM	100	94		[65]
AID line probe assay	Multiplex PCR and reverse hybridization with carbapenemases probes	5 h	Various clinical specimens	KPC, IMP, VIM, VIM, NDM, OXA-48, SIM, SPM, AIM, BIC, DIM, GIM, IMI, NMC-A	97.7	-		[66]
Hyplex MBL ID system	Multiplex PCR and reverse hybridization with carbapenemases	6 h	Various clinical specimens	VIM and IMP	98.0	98.6		[67]

Xpert® Carba-R Assay detects resistance genes in carbapenemase-producing bacteria

- Cartridge detects five classes of carbapenem resistance genes (>95):
  - $bla_{KPC,}$ $bla_{NDM,}$ $bla_{VIM,}$ $bla_{OXA-48,}$ bla_{IMP}
  - Time to result: 50 minutes

- **Sample types**:
  - Rectal swabs
  - Peri-rectal swabs
  - Carbapenem non-susceptible, pure colonies
    * Can be used to formulate therapeutic strategies

(**Rectal and peri-rectal swabs cannot be used to formulate therapeutic strategies)

US-IVD and CE-IVD. In Vitro Diagnostic Medical Device. May not be available in all countries.

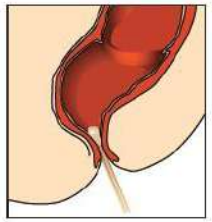
Rectal/Perirectal Swab Specimen Collection Protocol

Rectal/Perirectal Specimen Collection

1 Use Cepheid Collection Device #900-0370 to collect the specimen.

Rectal Swab Sample

Carefully insert both swab tips approximately 1 cm beyond the anal sphincter and rotate gently.

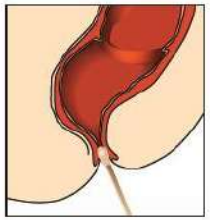


2 OR

CE-IVD. For *in-vitro* diagnostic use

Perirectal Swab Sample

Carefully insert both swab tips no more than 1 cm into the anal opening before the anal sphincter and rotate gently.



3 Place the swab pair back into the transport tube.

4 Swabs in the transport tube can be stored at 15-28 °C for up to five days.

In Vitro Diagnostic Medical Device IVD CE IVD

301-6889, Rev. B February 2018

Cepheid. A better way.

Possible Algorithm in Case of Suspicion of CPE

Following ECDC Guidance[1,2]

High-Risk Patients

- Previous inpatient **overnight stay** in a healthcare setting within the last 12 months
- Had **multiple hospital treatments**, e.g., dialysis, chemo-therapy, in last 12 months
- All admissions to **high-risk setting**, e.g., ICU and onco-haematology units
- Previously been **identified as CPE positive**, in last 12 months
- **Contact patients** in case of outbreak/known case of CPE
- To consider: Patients who **travelled abroad** and fragile patients having **previously received carbapenem** treatment

Patient **preemptively** in contact precaution (CP)* and isolated

Rectal/Perirectal swab x1

Rapid molecular: Xpert Carba-R

50 mins

Negative Result

Positive Result

Stop CP*, Patient **removed** from isolation

Patient **remains** in CP* and isolated (cohorting possible)

- Dedicated and increased staffing
- Weekly screening
- Computer identification
- Initiate **contact tracing**

1. ECDC RAPID RISK ASSESSMENT. Carbapenem-resistant Enterobacteriaceae–second update. 26 Sept. 2019. Accessed June 2020 https://www.ecdc.europa.eu/sites/portal/files/documents/carbapenem-resistant-enterobacteriaceae-risk-assessment-rev-2.pdf
2. Magiorakos A.P, et al. Infection prevention and control measures and tools for the prevention of entry of carbapenem-resistant Enterobacteriaceae into healthcare settings: guidance from the European Centre for Disease Prevention and Control. Antimicrobial Resistance and Infection Control (2017) 6:113

*CP = contact precaution: reinforced hand washing, wearing of apron, warning, dedicated equipment, proper use of gloves, reinforced environmental disinfection

Who to test? Varies by country and setting

India

Table 11.1: Antimicrobial prophylaxis and surveillance in HSCT patients

Policy	Details	Comments
	BMT pre-engraftment	
Antibiotic prophylaxis	No antibiotic prophylaxis is given	
Surveillance culture	Stool surveillance culture for multidrug resistant bacteria in stool and throat swab samples may be done to detect colonization with MDR bacteria. Note this should not be used to initiate prophylaxis	This detects ESBL, AmpC, carbapenemase producers, MRSA and VRE. However patients colonized with resistant pathogens should not be presumed to be the only cause of fever without microbiological confirmation
Surveillance PCR for MDRO colonization	Stool and throat swab samples from patients may be screened for the presence of genes indicating colonization with MDR bacteria	These real-time PCR or end point multiplex PCR based tests can detect NDM, OXA-48, KPC, IMP-1 and VIM genes associated with carbapenem resistance and mecA genes and VanA or vanB genes encoding for MRSA and VRE respectively.
Antifungal prophylaxis	Posaconazole	This may be administered IV/oral. Blood levels may be monitored if TDM (Therapeutic Drug Level) monitoring

Treatment guidelines for antimicrobial use in common syndromes ICMR 2019 https://main.icmr.nic.in/sites/default/files/guidelines/Treatment_Guidelines_2019_Final.pdf Last accessed Feb.6, 2022.

Italy


Ambretti et al. Antimicrobial Resistance and Infection Control (2019) 8:136
https://doi.org/10.1186/s13756-019-0591-6

Antimicrobial Resistance and Infection Control

REVIEW Open Access

Screening for carriage of carbapenem-resistant Enterobacteriaceae in settings of high endemicity: a position paper from an Italian working group on CRE infections

Simone Ambretti[1*], Matteo Bassetti[2], Pierangelo Clerici[3], Nicola Petrosillo[4], Fabio Tumietto[5], Pierluigi Viale[6] and Gian Maria Rossolini[6]

Candidate patient categories for screening upon admission to acute-care hospitals

- Patients from long-term care and rehabilitation facilities
- Patients transferred from another acute-care hospital
- Patients with a history of hospital admission during the previous 12 months

Ambretti et al ARIC 2019. Last accessed Feb.6, 2022

MRSA Screening

Dr. Debkishore Gupta

S. aureus and SSIs—An Avoidable Threat?

Most SSIs can be prevented through successful implementation of clinical guidelines.

S. aureus colonized patients are up to 9 times more likely to develop an SSI

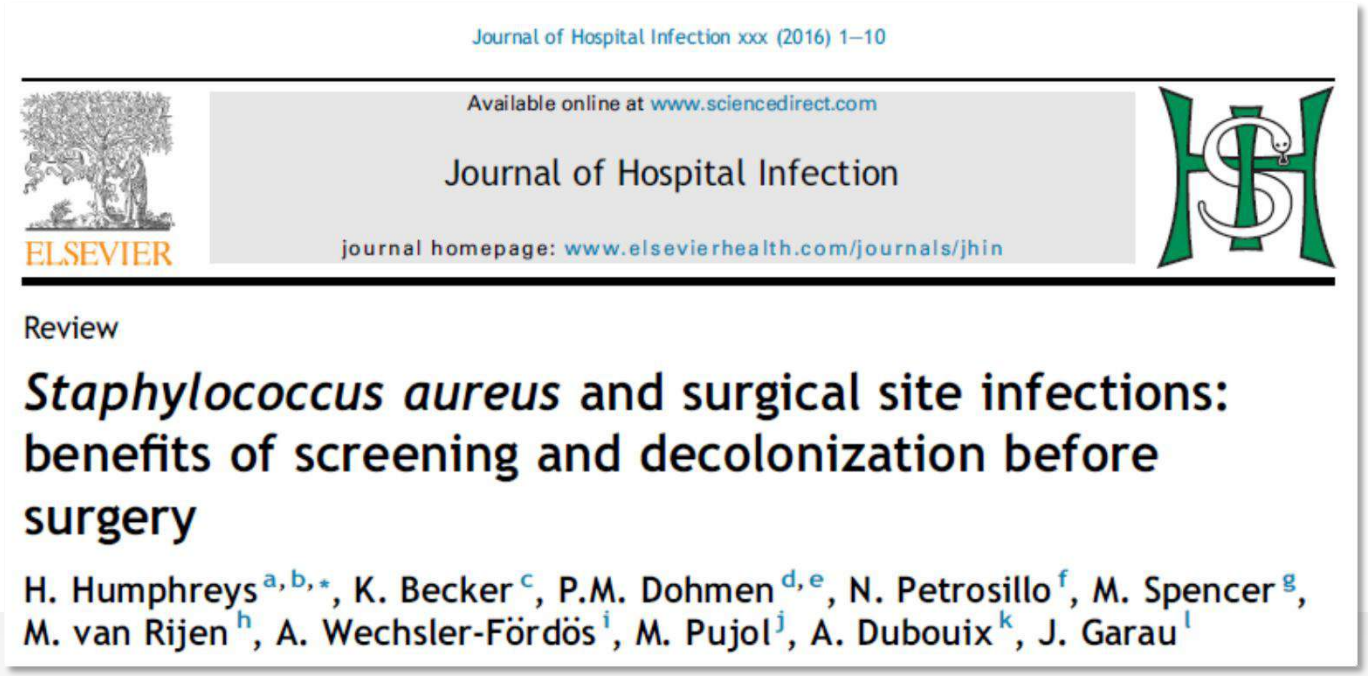
Majority of *S. aureus* cases are endogenous (originate in patient's own flora)

Strategies should therefore focus on preventing infections through eliminating nasal carriage, such as with pre-surgical screening and decolonization

Health First Europe. 2020. Insight Report: Identifying the gaps between evidence and practice in the prevention of surgical site infections. Accessed Jul 2021. http://healthfirsteurope.eu/wp-content/uploads/2020/11/A3A4-8pp-Booklet-English-Spreads.pdf

Humphreys H, et al. *Staphylococcus aureus* and surgical site infections: benefits of screening and decolonization before surgery. J Hosp Infect. 2016 Nov;94(3):295-304.

Impact of *S. aureus* and SSIs



Journal of Hospital Infection xxx (2016) 1–10

Available online at www.sciencedirect.com

Journal of Hospital Infection

journal homepage: www.elsevierhealth.com/journals/jhin

Review

Staphylococcus aureus and surgical site infections: benefits of screening and decolonization before surgery

H. Humphreys[a,b,*], K. Becker[c], P.M. Dohmen[d,e], N. Petrosillo[f], M. Spencer[g], M. van Rijen[h], A. Wechsler-Fördös[i], M. Pujol[j], A. Dubouix[k], J. Garau[l]

> The mean postoperative **length of stay (LOS) is 10 days for SSIs**, with a resultant additional healthcare cost.

SSI LOS examples:

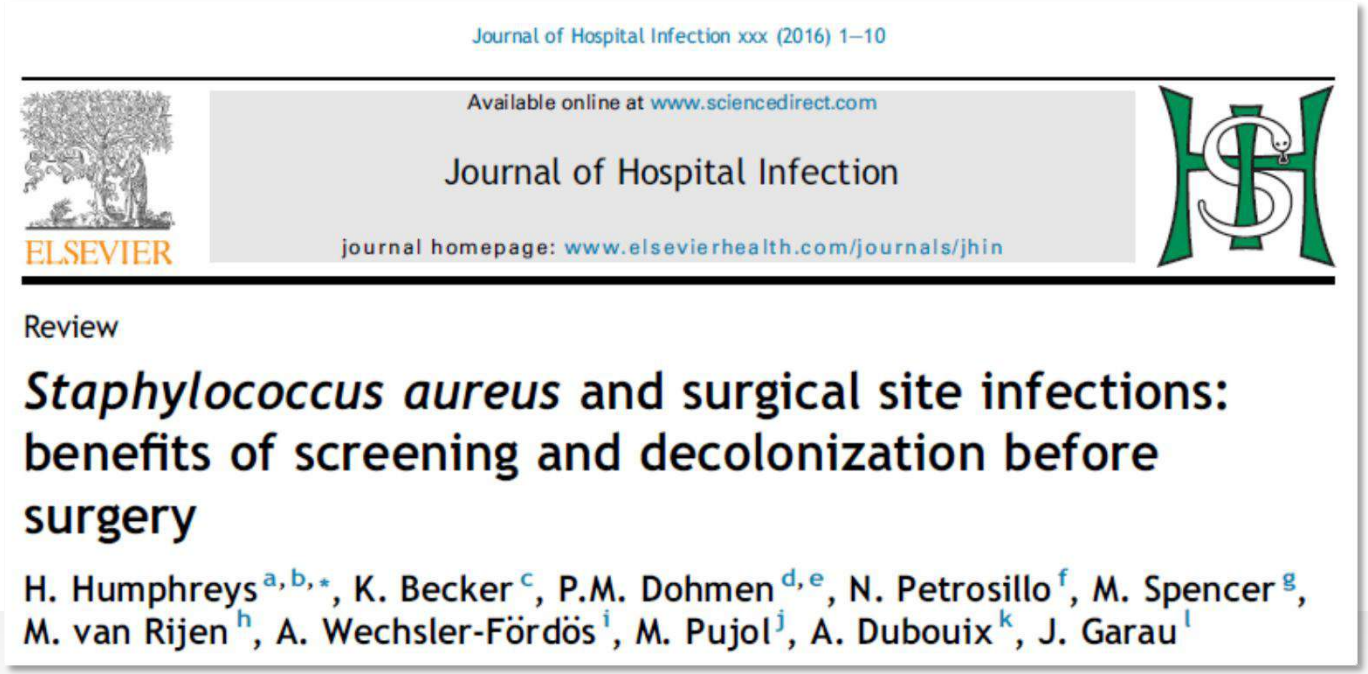
- ✓ Cardiac Surgery: **23 days**
- ✓ Vascular Procedures: **10 days**
- ✓ Hip Replacement: **17 days**

Resource-rich countries → SSIs are the third most common cause of HAIs.
Income-poor countries → SSIs are the most common cause of HAIs.

Yarbrough M, et al. Multicenter evaluation of the Xpert MRSA NxG assay for detection of methicillin-resistant *Staphylococcus aureus* in Nasal Swabs. J Clin Microbiol. 2017 Dec;56(1).

CE-IVD. *In Vitro* Diagnostic Medical Device. Not available in all countries.

Key Recommendations by European and US Experts



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Review

Staphylococcus aureus and surgical site infections: benefits of screening and decolonization before surgery

H. Humphreys[a,b,*], K. Becker[c], P.M. Dohmen[d,e], N. Petrosillo[f], M. Spencer[g], M. van Rijen[h], A. Wechsler-Fördös[i], M. Pujol[j], A. Dubouix[k], J. Garau[l]

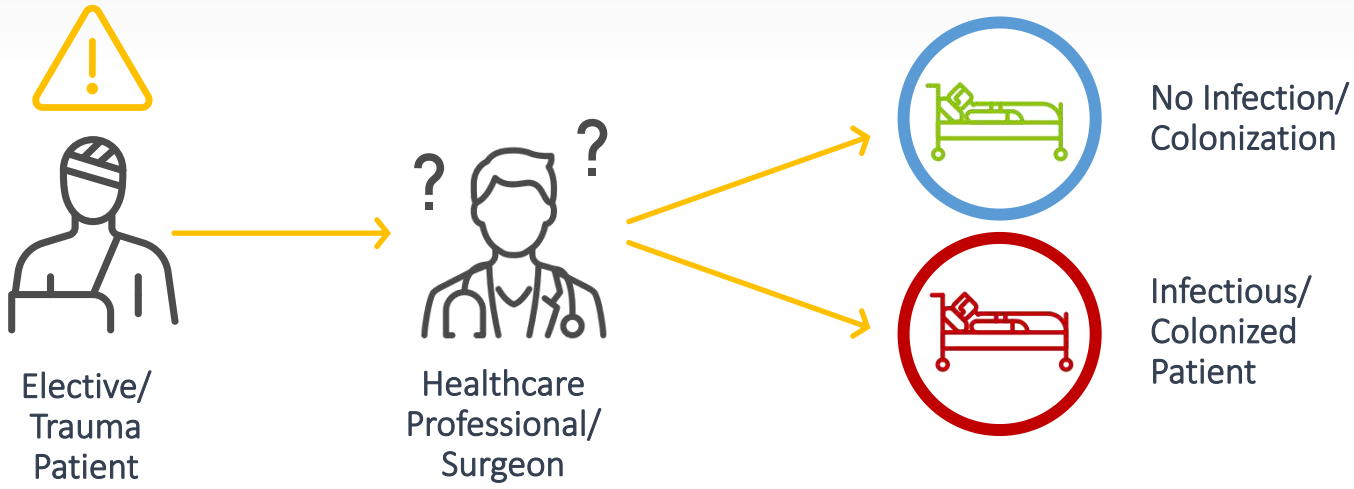
> Pre-operative screening… and subsequent decolonization of patients who are positive MSSA and MRSA reduces SSIs and hospital stay. This applies especially to major clean surgery, such as cardiothoracic and orthopedic.

1. Screening & selective decolonization → Reduces SSIs, costs, and new resistances.
2. Avoid empirical decolonization → Increases in resistances.
3. Targeted decolonization with Mupirocin & Chlorhexidine → Effective in reducing SSIs.

Humphreys H, et al. *Staphylococcus aureus* and surgical site infections: benefits of screening and decolonization before surgery. J Hosp Infect. 2016 Nov;94(3):295-304.

Challenges of *S. aureus* Testing and Patient Management

Time matters, now more than ever →
How to get surgical patients in and out—quickly, safely, and infection free?



Culture Results:
Take up to 72+ Hours[1]

Inappropriate Decolonization or
Non-Adherence[2]

Delayed Surgery or
Proceed Before Results[2]

→ High Costs for Hospitals

1. Yarbrough M, et al. Multicenter evaluation of the Xpert MRSA NxG assay for detection of methicillin-resistant *Staphylococcus aureus* in Nasal Swabs. J Clin Microbiol. 2017 Dec;56(1).
2. Bouza E, et al. Colonization of the nasal airways by *Staphylococcus aureus* on admission to a major heart surgery operating room: A real-world experience. Enfermedades Infecciosas y Microbiología Clínica. 2020 Dec;38(10):466-470.

Broad Coverage for Reliable Performance

1

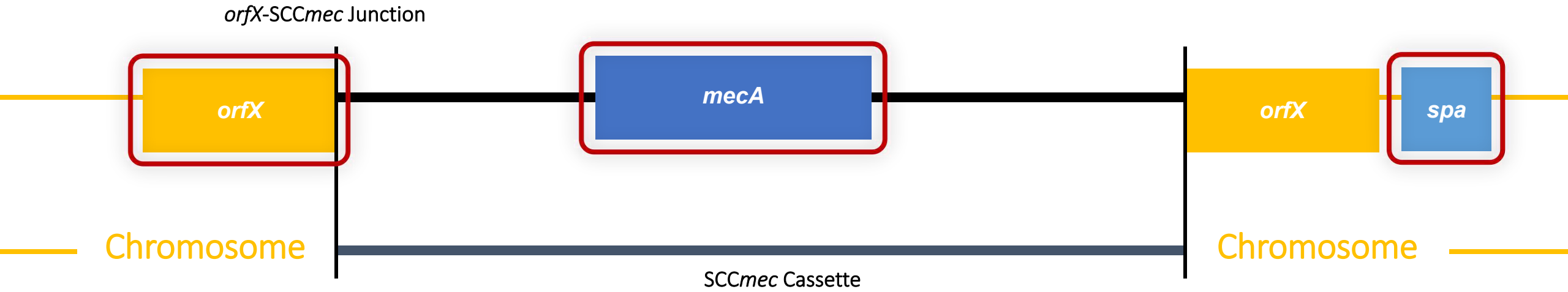
Insert Swab into Sample Reagent and Vortex.

2

Transfer the Sample Reagent to the Cartridge.

3

Insert Cartridge and Start Test.



Xpert® SA Nasal Complete—see Product Insert (301-0189, Rev. G January 2020) for additional details.
CE-IVD. *In Vitro* Diagnostic Medical Device. Not available in all countries.

(Xpert® *SA Nasal Complete*)

VRE Screening

Dr. Debkishore Gupta

Example high-risk groups (stepping-stones) recommended for screening.

Previous inpatient in any hospital, including abroad, in last 12 months

All admissions to augmented care or high-risk settings, e.g., ICU

Previously been identified as VRE positive, in last 12 months

Had multiple hospital treatments, e.g., hemodialysis, chemotherapy

Contact patients in case of outbreak/known case of VRE

CDC. 2010. Vancomycin-resistant Enterococci (VRE) and the Clinical Laboratory. Accessed Mar 2021. https://www.cdc.gov/hai/settings/lab/vreclinical-laboratory.html.

Jaureguy F, et al. Impact of the Cepheid Xpert® *vanA/vanB* on the management of patients at risk of carrying glycopeptide-resistant enterococci. Poster presented at ECCMID 2016, Apr 9-12, Amsterdam, Netherlands.

Haut Conseil de Santé Public. Actualisation des recommandations relatives à la maîtrise de la diffusion des bactéries hautement résistantes aux antibiotiques émergentes (BHRe). Décembre 2019.

Birgand G, et al. Cost associated with implementation of a strict policy for controlling spread of highly resistant microorganisms in France. BMJ Open. 2016 Jan;6:e009029.

Detect *vanA* and *vanB* Genes in 48 Minutes

1

Insert Swab into Sample Reagent and Vortex.

2

Transfer the Sample Reagent to the Cartridge.

3

Insert Cartridge and Start Test.

Sensitivity*		Positive Predictive Value*	
vanA/vanB			
Rectal	Perianal	Rectal	Perianal
99.0%	92.9%	37.2%	55.3%
96.7%		42.0%	

Specificity*		Negative Predictive Value*	
vanA/vanB			
Rectal	Perianal	Rectal	Perianal
79.3%	88.7%	99.8%	98.8%
82.3%		99.5%	

Note regarding PPV:

- Other normal inhabitants of the gut flora may exhibit *vanB* genes which can still be detected by PCR[1]

Focus should be on NPV:

- Excellent NPV = Negative results can be relied upon for informed early decision making[2]

1. Marcadé G, et al. Outbreak in a unit involving an unusual strain of glycopeptide-resistant *Enterococcus faecium* carrying both *vanA* and *vanB* genes. Journal of Antimicrobial Chemotherapy. 2014 Feb;69(2):500–505.
2. Saliba, R et al. Can real-time polymerase chain reaction allow a faster recovery of hospital activity in cases of an incidental discovery of CPE and VRE Carriers? J Hosp Infect. 2019 Oct;103(2):115-120.
See Xpert® *vanA/vanB* Product Insert (301-0188 Rev. D April 2019) for additional details.
CE-IVD. *In Vitro* Diagnostic Medical Device. Not available in all countries.

Therapeutic Strategy/ Precision Medicine

Dr. Debkishore Gupta

Therapy Management of CPE

Recommended treatment for CPE infection[1]

- Combinatory therapies with at least two drugs → greater effectiveness in critically-ill patients

Colistin monotherapy is not recommended[1]

- Nephrotoxic and to a lesser extent neurological toxicity
- Poor pulmonary penetration

New drugs have been launched = antibiotic/β-lactamase inhibitor combinations

→Not effective against all classes of CPE

Rapid diagnostic tests differentiating the carbapenemase genes should be integrated into antimicrobial stewardship programs to impact patient management and therapeutic choices in a timely manner[2,3]

1. Reyes J, et al. Carbapenem-Resistant Klebsiella pneumoniae: Microbiology Key Points for Clinical Practice. Int J Gen Med. 2019 Nov 28;12:437-446.
2. Doi Y, et al. Treatment Options for Carbapenem-resistant Gram-negative Bacterial Infections. Clin Infect Dis. 2019 Nov 13;69(Supplement_7):S565-S575
3. Falcone M, et al. Time to appropriate antibiotic therapy is a predictor of outcome in patients with bloodstream infection caused by KPC-producing Klebsiella pneumoniae. Crit Care. 2020 Jan 30;24(1):29. Last accessed Feb.6, 2022.

Supporting Appropriate Therapeutic Strategies*

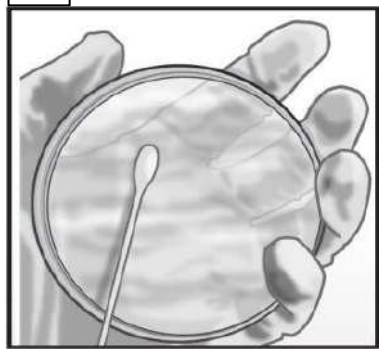
- The identification of a *bla*$_{IMP}$, *bla*$_{NDM}$, or *bla*$_{VIM}$ metallo-beta-lactamase gene may be used as an **aid to clinicians in determining appropriate therapeutic strategies** for patients with known or suspected carbapenem-non-susceptible bacterial infections
- *From testing **pure colonies** with Xpert® Carba-R

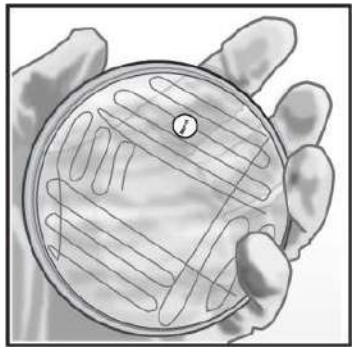
THINK → Which antibiotics won't work, NOT which will work.

*From testing pure colonies with Xpert® Carba-R. See Xpert® Carba-R Product Insert (301-9242, Rev. C June 2020) for additional details.
CE-IVD. *In Vitro* Diagnostic Medical Device. Not available in all countries.

Bacterial Isolate Sample Preparation

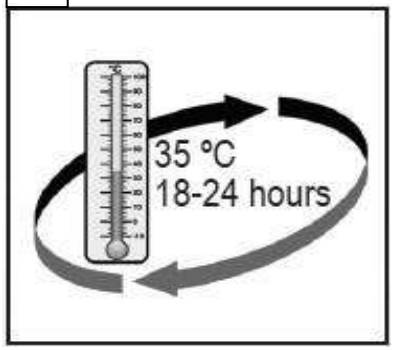
1





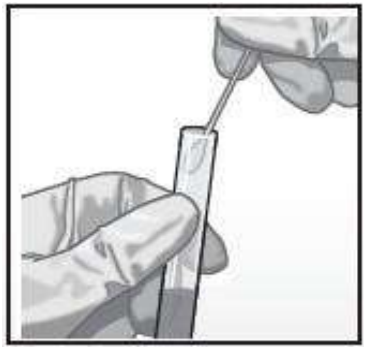
Inoculate the organism onto either a blood or MacConkey agar plate, streak for isolation and place a 10 µg meropenem disk in the first streak quadrant to ensure that the isolate is still carbapenem-non-susceptible.

2



Incubate the plate at 35 ºC for 18-24 hours in the ambient air.

3



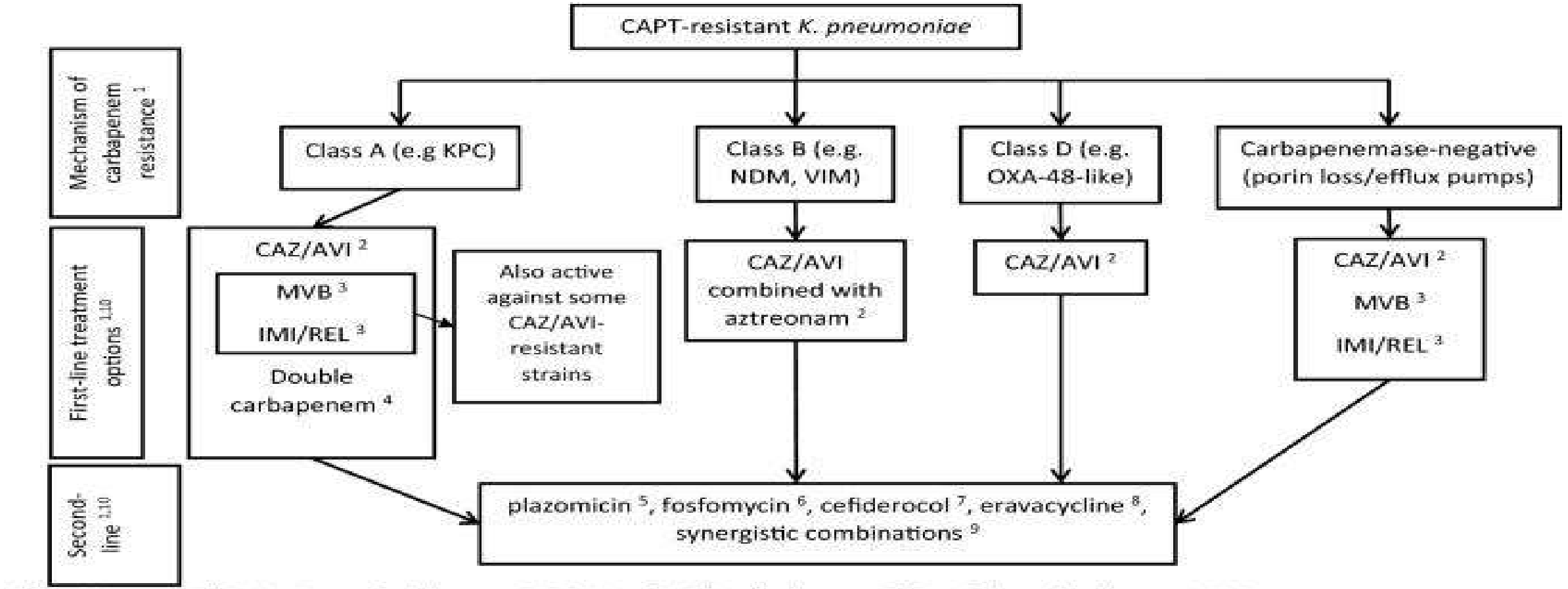
Use the direct colony suspension method by touching isolated colonies with a swab or loop to prepare a 0.5 McFarland suspension of the bacterial isolate. Refer to the package insert for further details.

New Antimicrobial Agents

Antimicrobial Agent	Company	EMA Status	KPC	NDM	IMP	VIM	OXA-48
CPE Class			A	B	B	B	D
Zavicefta Ceftazidime-avibactam	Pfizer	Approved for complicated UTI, complicated IAI in combination with metronidazole	Yes	No	No	No	Limited
Vaborem Meropenem-vaborbactam	MENARINI	Approved for complicated UTI including pyelonephritis	Yes	No	No	No	No
Zerbaxa Ceftolozane-tazobactam	MERCK	Approved for HABP and VAP, complicated UTI, complicated IAI	No	No	No	No	No
Recarbrio Imipenem-cilastatin-relebactam	MERCK	Approved for complicated UTI including pyelonephritis	Yes	No	No	No	No
Fetroja Cefiderocol Cephalosporin-siderophore	SHIONOGI	Approved for complicated UTI including pyelonephritis	Yes	Yes	Yes	Yes	Yes
Aztreonam-avibactam	Pfizer	Phase 3 clinical trials	Yes	Yes	Yes	Yes	Yes

EMA: European Medicines Agency
UTI, urinary tract infection; IAI, intraabdominal infection; HABP, hospital acquires bacterial pneumonia; VAP, ventilator associated pneumoniae
https://www.ema.europa.eu/en/search/search/field_ema_web_categories%253Aname_field/Human? accessed 06-04-2020

Enzyme based therapy: XDR-Klebsiella

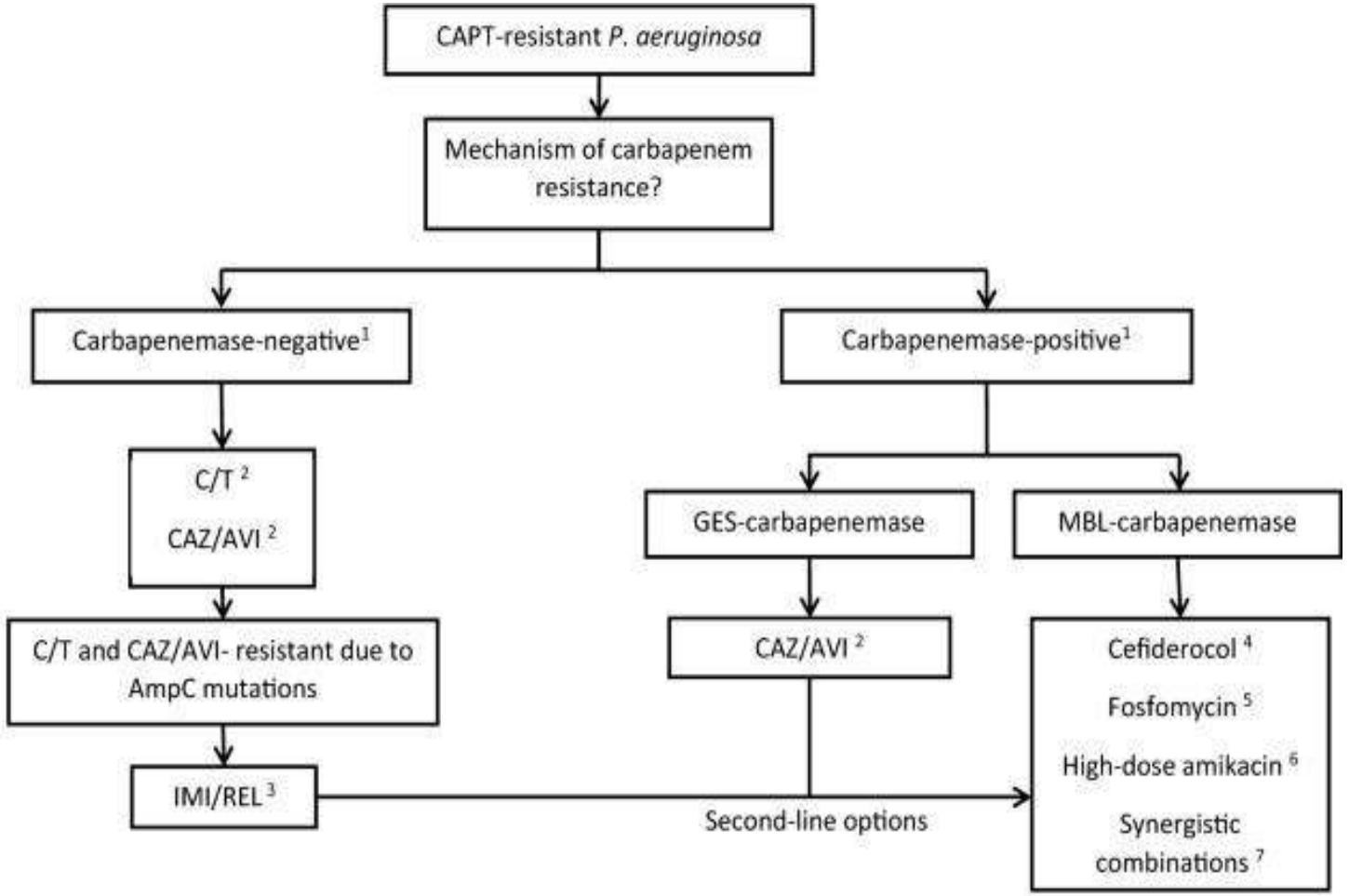


Abbreviations; IMI/REL= imipenem/relebactam, CAZ/AVI= ceftazidime/avibactam, C/T= ceftolozan/tazobactam, MVB= meropenem/vaborbactam

Carbapenems, Aminoglycosides, Polymyxins and Tigecycline (CAPT-resistant)

Karakonstantis et al: Treatment options for K. pneumoniae, P. aeruginosa and A. baumannii co- resistant to carbapenems, aminoglycosides, polymyxins and tigecycline: an approach based on the mechanisms of resistance to carbapenems. Infection (2020) 48:835–851 https://doi.org/10.1007/s15010-020-01520-6. Last accessed Feb. 6, 2022.

Enzyme based therapy: XDR-Pseudomonas



Abbreviations; IMI/REL= imipenem/relebactam, CAZ/AVI= ceftazidime/avibactam, C/T= ceftolozan/tazobactam, MVB= meropenem/vaborbactam

Carbapenems, Aminoglycosides, Polymyxins and Tigecycline (CAPT-resistant)

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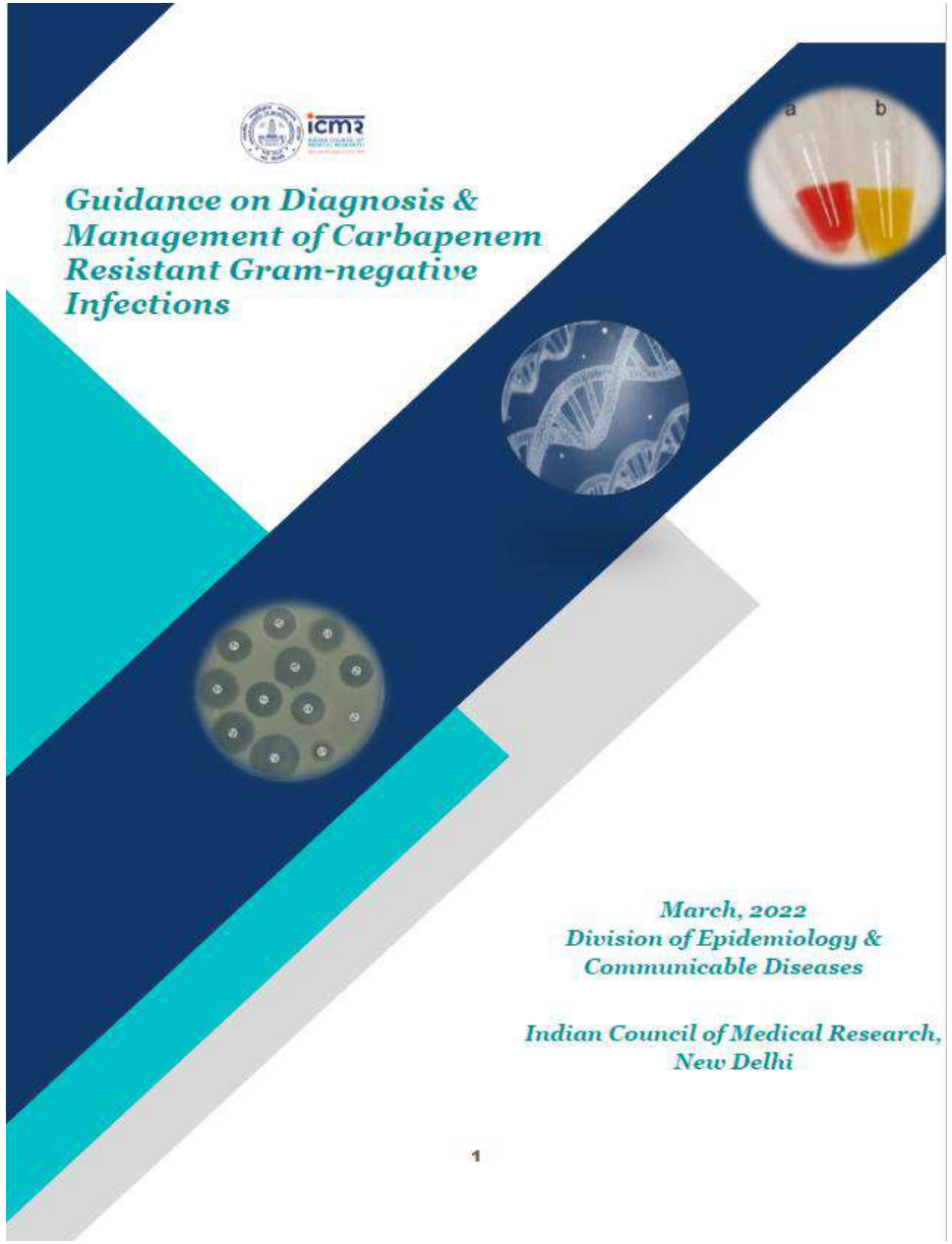


Table 2: Characteristics of commercial carbapenemase detection assays that have been approved for detection of carbapenemases in CRE isolates

Assay	Method	Time of results	Source	Detection of carbapenemases gene	Sensitivity (%)	Specificity (%)	Approval
Xpert Carba-R®	Real time multiplex PCR	2 hrs	Isolate	KPC, IMP, VIM, NDM, OXA-48 like	100	100	CE-IVD FDA IVD
BioFire film Array®	Real-time PCR	1-2 h	Positive blood culture	KPC	NA	NA	CE-IVD FDA IVD
Nanosphere Verigene BC-GN®	Microarray	2 h	Positive blood culture	KPC, NDM, VIM, IMP, OXA	NA	NA	CE-IVD FDA IVD
EntericBio CPE® assay	Real time multiplex PCR	2 h	Isolate, swabs	KPC, IMP, VIM, NDM, OXA-48 like, GES-5, IMI, OXA-23	100	100	RUO
Check- Direct CPE® assay	Real time multiplex PCR	3.5 h	Rectal swab/ Isolate	KPC, OXA-48 including OXA-181, VIM and NDM	100	94%	RUO
AID® line probe assay	Multiplex PCR and reverse hybridization with carbapenemases probes	5 h	Various clinical specimens	KPC, IMP, VIM, NDM, OXA-48, SIM, SPM, AIM, BIC, DIM, GIM, IMI, NMC-A	97.7	NA	RUO
Hyplex MBL ID® system	Multiplex PCR and reverse hybridization with carbapenemases probes	5 h	Various clinical specimens	VIM and IMP	98	98.6	RUO
BB MAX™ CRE Assay®	Real-time PCR	2 h	Rectal swab/ Isolate	KPC, NDM, oxa-48	93.1	97.3	RUO
Check-MDR 103 XL	PCR followed by microarray	6.5 h	Isolate	KPC, OXA-48, VIM, NDM, GES, GIM, SPM, OXA-23 like, Oxa-24 like	100	100	RUO
Eazyplex® SuperBug CRE®	Loop mediated	15 min	Positive blood	KPC, NDM, VIM	100	100	RUO

NA – not available; RUO – research use only; FDA - Food and Drug Administration; CE-IVD - Conformite Europeene *in-vitro* diagnostic

C. difficile testing

Dr. Debkishore Gupta

Challenges of CDI Testing and Patient Management 1/2

Time matters, now more than ever →
Too many patients, not enough isolation beds.

Toxigenic culture is not practical for routine use[1]

Toxin/GDH tests are not sensitive/specific enough for standalone use[1,2]

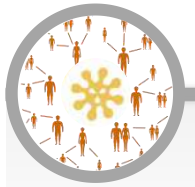
Algorithmic testing can delay correct patient care[3]

→ High Costs for Hospitals

CDI-C.difficile infection

1. Carroll K & Mizusawa M. Laboratory tests for the diagnosis of *Clostridium difficile*. Clin Colon Rectal Surg. 2020 Mar;33(2):73-81.
2. Casari E, et al. Reducing rates of *C. difficile* infection by switching to a stand-alone NAAT with clear sampling criteria. Antimicrob Resist Infect Control. 2018 Mar;7(40).
3. Peppard W, et al. Implementation of polymerase chain reaction to rule out *C. difficile* infection is associated with reduced empiric antibiotic duration of therapy. Hosp Pharm. 2014 Jul;49(7):639-43.

Challenges of CDI Testing and Patient Management 2/2



Underdiagnosis of CDI →

- Delays in treatment and a poor clinical outcome
- Disease transmission and associated infection-related costs and outcomes

Overdiagnosis of CDI →

- Testing of inappropriate stool samples
- Importance of stool consistency
- Unnecessary antibiotic treatment and antibiotic-related adverse events

Rapid and accurate diagnosis is essential for:
1) Effective infection control measures, and **2)** Implementation of appropriate therapy.

McDonald L, et al. Clinical Practice Guidelines for *Clostridium difficile* Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). Clin Infect Dis. 2018 Apr;66(7):e1–e48.

COVID-19 Impact on CDI

Increased empirical prescribing + broad-spectrum antibiotics → CDI threat grows.

Rise in broad-spectrum antibiotics → Serious concerns about rapid spike in CDI

Frequent empirical therapy (e.g., moxifloxacin) → Drugs strongly associated with CDI

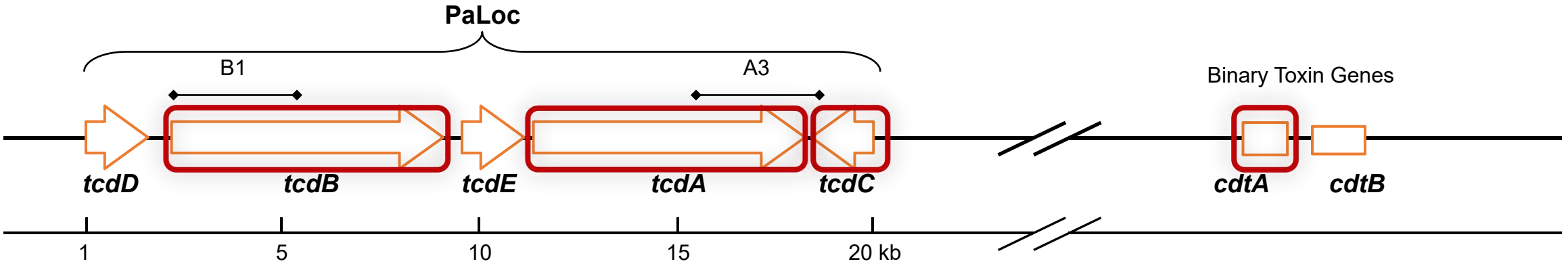
Increased CDI vigilance and diagnosis are necessary to ensure appropriate treatment and improve outcomes.

Spigaglia P. COVID-19 and *Clostridioides difficile* infection (CDI): possible implications for elderly patients. Anaerobe. 2020 Aug;64:102233.

Ferreira E, et al. Should we be worried about *Clostridioides difficile* during the SARS-CoV2 Pandemic? Front Microbiol. 2020 Sep;11:2292.

CDI- Virulence Factors

- Major virulence factors for CDI → Toxins A and B (encoded by *tcdA* and *tcdB* genes)
- Additional virulence factors:
  - Deletion of the nucleotide at position 117 of the *tcdC* gene → Consistent with Ribotype 027 strains (associated with higher CDI severity)
  - Binary toxin (encoded on *cdtA* and *cdtB* genes)



Guery B, et al. *Clostridioides difficile*: diagnosis and treatments. BMJ 2019. Aug;20(366):4609.
Marujo V, et al. The largely unnoticed spread of *Clostridioides difficile* PCR ribotype 027 in Germany after 2010. IPIP. 2020 Dec;2(4):100102.

Broad Coverage for Reliable Performance (Xpert® *C. difficile* BT)

1

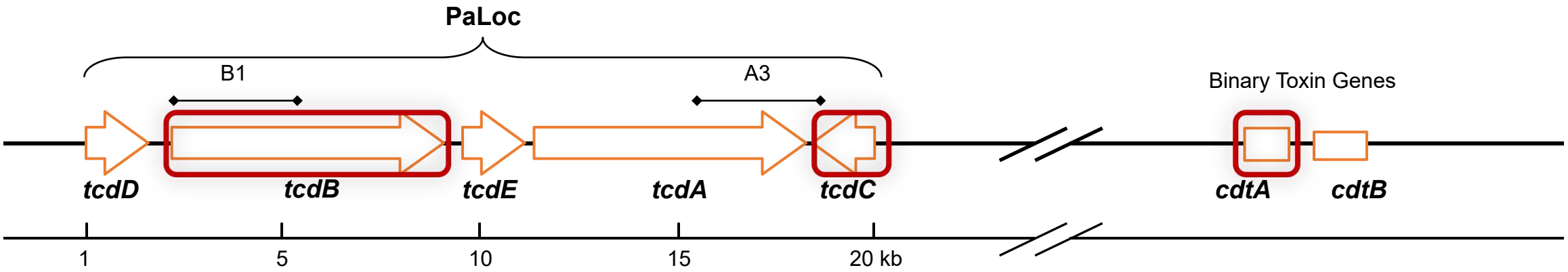
Insert Swab into Sample Reagent and Vortex.

2

Transfer the Sample Reagent to the Cartridge.

3

Insert Cartridge and Start Test.



See Xpert® *C. difficile* BT Product Insert (301-6190, Rev. C, May 2020) for additional details.
CE-IVD. *In Vitro* Diagnostic Medical Device. Not available in all countries.

Binary Toxin and 027 Strain May Be Important

1

Infections with ribotype 027 can independently predict severe CDI and mortality[1,2]

2

There is evidence to suggest binary toxin can contribute to CDI severity and recurrence[3]

"Binary toxin either is a marker for more virulent *C. difficile* strains or contributes directly to strain virulence"

3

Strains have been reported as negative for toxin A/B <u>but</u> positive for binary toxin, yet have caused CDI[4,5]

These strains would be missed by common Toxin EIA and other molecular-based tests

1. Rao K, et al. *C. difficile* ribotype 027: relationship to age, detectability of toxins A or B in stool with rapid testing, severe infection, and mortality. Clin Infect Dis. 2015 Jul 15;61(2):233-41.
2. Marujo V, et al. The largely unnoticed spread of *Clostridioides difficile* PCR ribotype 027 in Germany after 2010. IPIP. 2020 Dec;2(4):100102.
3. Stewart D, et al. Predicting recurrence of *C. difficile* colitis using bacterial virulence factors: binary toxin is the key. J Gastrointest Surg. 2013 Jan;17:118-24.
4. Eckert C, et al. Prevalence and pathogenicity of binary toxin-positive *C. difficile* strains that do not produce toxins A and B. New Microbes New Infect. 2014 Nov;3:12-7.
5. Androga G, et al. Evaluation of the Cepheid Xpert *C. difficile/Epi* and Meridian Bioscience Illumigene *C. difficile* assays for detecting *Clostridium difficile* ribotype 033 strains. J Clin Microbiol. 2015 Mar;53(3):973-5.

How to Implement a mRDT in your Hospital?

- Provide baseline prevalence of MDR-GNB, stratified for different organisms, antimicrobial agents, and resistance determinants
- Describe availability of laboratory personnel during the study
- Consider reporting of time from identification/AST in the lab to actual therapy adjustments
- Include detailed sample size calculations for the different endpoints, including development of resistance
- Provide clear definitions of the study population and subgroups
- Consider to possibly assess clinical outcomes following rapid test-driven therapeutic choices as a measure to explore diagnostic performances in an adequate sample of patients without conventional microbiological diagnosis.
- Consider direct comparison between rapid tests and of combinations of rapid tests.

Giacobbe et al. Rapid microbiological tests for bloodstream infections due to multidrug resistant Gram-negative bacteria: therapeutic implications, Clinical Microbiology and Infection, https://doi.org/10.1016/j.cmi.2019.09.023.

How to Implement a mRDT in your Hospital?

Important factors to be considered when implementing rapid tests within local diagnostic protocols

- Molecular rapid tests generally identify a limited spectrum of microorganisms and of resistance mechanisms.
- Results of molecular AST are a useful proxy but not a definite proof of resistance.
- Molecular AST provide qualitative but not quantitative results.
- Rapid identification of specific resistance mechanisms will likely be more essential in the future, because of the specific activity of some novel agents against different types of resistance mechanisms.
- Economic costs and personnel availability need to be necessarily taken into account when implementing one or more novel rapid tests into the laboratory workflow.
- Consider prioritization of specific patients' categories and wards of patients at risk to maximize cost-effectiveness.
- Consider feasibility of implementation of a 24/7 laboratory service.

Giacobbe et al. Rapid microbiological tests for bloodstream infections due to multidrug resistant Gram-negative bacteria: therapeutic implications, Clinical Microbiology and Infection, https://doi.org/10.1016/j.cmi.2019.09.023.

Summary of Utility of Molecular Diagnostics

1. Feasibility of quicker screening in high-risk population
2. Fast molecular methods offer the possibility of syndromic testing and enables **early action** for maximum impact
3. Detection of resistance mechanisms – Carbapenemase detection – can facilitate “personalized” antibiotic regimen (precision medicine) = appropriate antibiotic choices
4. The “advantages” of molecular tests result in significant improvement in clinical outcomes ONLY when combined with a systematic implementation into the workflow
5. **Hence, mRDT should be implemented as an essential component of a well functioning ASP**

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Thank You

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