



Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

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

Review

Diagnosis and management of infections caused by multidrug-resistant bacteria: guideline endorsed by the Italian Society of Infection and Tropical Diseases (SIMIT), the Italian Society of Anti-Infective Therapy (SITA), the Italian Group for Antimicrobial Stewardship (GISA), the Italian Association of Clinical Microbiologists (AMCLI) and the Italian Society of Microbiology (SIM)



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Abbreviations: AMR, Antimicrobial resistance; ASP, antimicrobial stewardship programmes; BAT, best available therapy; BSI, bloodstream infection; CRAB, carbapenem resistant *Acinetobacter baumannii*; CRE, carbapenem resistant Enterobacterales; CR-GNB, carbapenem-resistant Gram negative bacilli; DTR-PA, difficult-to-treat *Pseudomonas aeruginosa*; ELF, epithelial lining fluid; ESBL, extended-spectrum β -lactamase; FUBC, follow-up blood cultures; ICU, intensive care unit; KPC, *Klebsiella pneumoniae* carbapenemase; MBL, metallo- β -lactamase; MDRO, Multidrug-resistant organisms; MRSA, methicillin resistant *Staphylococcus aureus*; NDM, New Delhi metallo- β lactamase; RCT, randomised controlled trial; RDT, rapid diagnostic tests; SSTI, skin and soft tissue infection; VAP, ventilator-associated pneumoniae; VIM, Verona integron-encoded metallo- β -lactamase.

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ARTICLE INFO

Article history:

Received 7 February 2022

Accepted 29 May 2022

Editor: Professor Jeffrey Lipman

Keywords:

Multidrug resistance

Treatment

Antimicrobial stewardship

ABSTRACT

Management of patients with infections caused by multidrug-resistant organisms is challenging and requires a multidisciplinary approach to achieve successful clinical outcomes. The aim of this paper is to provide recommendations for the diagnosis and optimal management of these infections, with a focus on targeted antibiotic therapy. The document was produced by a panel of experts nominated by the five endorsing Italian societies, namely the Italian Association of Clinical Microbiologists (AMCLI), the Italian Group for Antimicrobial Stewardship (GISA), the Italian Society of Microbiology (SIM), the Italian Society of Infectious and Tropical Diseases (SIMIT) and the Italian Society of Anti-Infective Therapy (SITA). Population, Intervention, Comparison and Outcomes (PICO) questions about microbiological diagnosis, pharmacological strategies and targeted antibiotic therapy were addressed for the following pathogens: carbapenem-resistant Enterobacterales; carbapenem-resistant *Pseudomonas aeruginosa*; carbapenem-resistant *Acinetobacter baumannii*; and methicillin-resistant *Staphylococcus aureus*. A systematic review of the literature published from January 2011 to November 2020 was guided by the PICO strategy. As data from randomised controlled trials (RCTs) were expected to be limited, observational studies were also reviewed. The certainty of evidence was classified using the GRADE approach. Recommendations were classified as strong or conditional. Detailed recommendations were formulated for each pathogen. The majority of available RCTs have serious risk of bias, and many observational studies have several limitations, including small sample size, retrospective design and presence of confounders. Thus, some recommendations are based on low or very-low certainty of evidence. Importantly, these recommendations should be continually updated to reflect emerging evidence from clinical studies and real-world experience.

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Introduction

Antimicrobial resistance (AMR) is one of the leading threats to human health and has been recognised by the World Health Organization (WHO) as a worldwide priority requiring urgent multisectoral action [1]. The WHO has recently launched a 'Call to Action on AMR' to enhance national and global efforts to tackle AMR through a One Health approach [2]. Misuse and overuse of antibiotics are the main drivers of the emergence and spread of AMR. Healthcare-associated infections caused by multidrug-resistant organisms (MDROs), including Gram-positive bacteria [methicillin-resistant *Staphylococcus aureus* (MRSA)] and Gram-negative bacilli [carbapenem-resistant *Pseudomonas aeruginosa* (CRPA), carbapenem-resistant *Acinetobacter baumannii* (CRAB) and carbapenem-resistant Enterobacterales (CRE)] are a leading cause of morbidity and mortality as well as increased healthcare costs all over the world [3]. The most recent European Antimicrobial Resistance Surveillance Network (EARS-Net) report highlighted a substantial proportion of MDROs spreading in several European Union/European Economic Area (EU/EEA) countries [4]. Although the percentage of resistant Gram-positive isolates has declined, MRSA remains an important pathogen in the EU/EEA, with levels still high in several countries [4]. The situation is more challenging for Gram-negative bacilli: more than one-half of the *Escherichia coli* and more than one-third of the *Klebsiella pneumoniae* isolates were resistant to at least one antimicrobial group [4]. Of note, an alarming increase in carbapenem resistance has been reported in several species, including *K. pneumoniae* (7.9% of isolates), *P. aeruginosa* (16.5% of isolates) and *A. baumannii* (>30% of isolates) [4]. CRE represent a significant threat to healthcare systems in all EU/EEA countries and the situation is endemic in some regions [5].

MDRO infections represent a clinical challenge because of limited treatment options, often including only last-resort antibiotics that are generally associated with high toxicity or poor efficacy. Although great efforts have been made to develop novel antibiotics to treat MDRO infections in recent years, the optimal management of these infections remains challenging, and some patients have no good treatment options for acute, life-threatening infections [6]. There are several challenges in the management of patients with

MDRO infections. First, expedited approval of new antibacterial agents is sometimes based on non-inferiority trials that exclude immunocompromised patients and those with severe infections, thereby limiting robust data regarding clinical efficacy against MDRO infections [7]. Meanwhile, old antibiotics are often associated with a high risk of side effects and were developed before the advent of a structured process for drug assessment and approval [8]. Moreover, the choice of antibiotic therapy is not the only factor associated with outcomes. Time to appropriate antibiotic therapy is one of the strongest predictors of mortality in patients with MDRO infections [9]. Thus, multifaceted strategies including implementation of infection control measures and antimicrobial stewardship programmes (ASPs), identification of patients at high risk of MDRO infections, and use of rapid diagnostic tests (RDTs) are needed to improve outcome while minimising the risk of emergence of resistance to new antibiotics. Rapid diagnosis of severe infections or sepsis is critical to improving patient management. However, the current standard of care often requires at least 48–72 h to provide useful results. One cause of delay in administration of optimal antibiotic therapy is the time required to identify pathogens and test antimicrobial susceptibility [10]. Recently, the development of new phenotypic and molecular technologies has improved the timing of microbiological diagnoses. A systematic review of 16 studies revealed that rapid phenotypic and molecular techniques reduce the time to administration of appropriate antibiotic therapy, especially when accompanied by effective communication [11,12]. Rapid identification of micro-organisms and characterisation of resistance can lead to earlier administration of appropriate antibiotic therapy and promotes de-escalation from broad-spectrum agents, potentially improves outcomes, causes fewer antibiotic therapy-related adverse effects, and reduces the incidence of antimicrobial-resistant micro-organisms.

The aim of this guidance is to assist clinicians in the management of patients with MDRO infections, with particular attention to microbiological diagnoses and antibiotic therapy. There are significant geographic differences in the molecular epidemiology of resistance and the availability of antibiotics. This document focuses on infections caused by MDROs in Europe, especially in countries with high prevalence of antimicrobial-resistant pathogens.

Methods

This guideline is the result of a joint effort by five Italian scientific societies, namely the Italian Association of Clinical Microbiologists (AMCLI), the Italian Group for Antimicrobial Stewardship (GISA), the Italian Society of Microbiology (SIM), the Italian Society of Infectious and Tropical Diseases (SIMIT) and the Italian Society of Anti-Infective Therapy (SITA).

As a preliminary step, a multidisciplinary panel was selected with expertise in clinical microbiology, infectious diseases and clinical pharmacology. The panel identified ten questions by consensus based on their perceived clinical relevance. Questions were formulated in Population, Intervention, Comparison and Outcomes (PICO) format and were appropriately modified, when necessary (Supplementary material). The output of this process informed the search strategy for a systematic review of the literature published between 1 January 2011 and 30 November 2020 in the PubMed and EMBASE databases by a subcommittee of the panel comprising two clinical microbiologists (GB and FG) and three infectious diseases specialists (DRG, AEM and GT). Relevant articles were retrieved following the hierarchy of evidence set by the Oxford Centre for Evidence-Based Medicine [13], with priority assigned to systematic reviews of randomised controlled trials (RCTs) and, alternatively, to individual RCTs; if these were not available, observational studies (individually or in the framework of systematic reviews with or without meta-analysis) were included. Only peer-reviewed articles in English were considered.

The subcommittee then drafted one or more recommendations for each question based on the literature identified. The supporting articles for all recommendations were assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system [14]. GRADE tables were prepared by assessing the certainty of evidence for each recommendation through the following domains: risk of bias; inconsistency; indirectness; and imprecision of the retrieved literature. Systematic reviews were evaluated using the Quality Assessment Tool provided by the US National Institutes of Health [15]; RCTs were evaluated according to the Effective Practice and Organisation of Care Guidelines [16]; observational studies were assessed with the Newcastle–Ottawa Scale (NOS) [17].

Overall, the strength of each recommendation was graded as ‘strong’ or ‘conditional’ (weak), whereas its certainty of evidence was graded as ‘high’, ‘moderate’, ‘low’ or ‘very low’. In the absence of sufficient evidence to use the GRADE system, good practice statements were produced based on expert consensus. The formulation of discordant recommendations (*strong recommendations with low-quality evidence*) was restricted to some specific cases, in which—despite the paucity of high-quality data—the panel provided recommendations about life-threatening situations or when there was high confidence that one option is potentially more risky than the other.

Voting panel members used a structured e-mail-based form to rate each statement on a five-point Likert-type scale indicating their level of agreement, from ‘strongly disagree’ (1) to ‘strongly agree’ (5). Results of 3 to 5 were defined as agreement, and consensus had been pre-determined as $\geq 90\%$ agreement. In case of disagreement, members could propose specific modifications to recommendations or to their level of strength or certainty, while providing justification.

Statements not reaching consensus at the first stage (~10%) were addressed in an online meeting of all the panel members who collectively revised the recommendations until a consensus was reached. The panel reviewed and approved the final statements, as modified in the consensus meeting.

This document only aims to address microbiological diagnosis and antimicrobial therapy; therefore, other aspects of infection

management (e.g. duration of antibiotic therapy) are not addressed. The focus is on invasive infections with MDROs as causative agents regardless of the source or the district. Where sufficient evidence was available to address a particular syndrome (e.g. pneumonia), specific recommendations are provided, otherwise they apply to invasive infections in general. Moreover, only adult patients with these infections are covered, thereby the recommendations presented in the next sections do not apply to paediatric subjects.

With regard to microbiological diagnosis, although there are no accepted criteria for the definition of rapid diagnostic tests (RDTs), pathogen-specific or syndrome-based tests are considered RDTs if they have relatively short performance times, yield results that may affect clinical decision-making, and support clinical management of patients. More specifically, we considered RDTs that have a turnaround time ≤ 8 h [18]. Studies evaluating the impact of both phenotypic and genotypic methods pointed to identify microorganisms as well as to evaluate antimicrobial susceptibility were included. To this regard, we included tests that look at the direct activity of antibiotics on bacteria (called phenotypic tests) and tests that search for particular genes in the bacteria to see whether they are expected to be susceptible or resistant to an antibiotic (called genotypic tests). During the development of this guideline, we did not discriminate between RDTs able to identify pathogens and RDTs able to identify molecular mechanisms of resistance. However, in each recommendation the role of molecular RDTs has been emphasised. Although the use of molecular RDTs may have higher costs and requires trained microbiologists, the aim of the present document is to highlight the important role of molecular RDTs and to encourage their use in the clinical practice.

Operational definitions informing specific aspects of recommendation development for each question are described as preamble in the corresponding section. The literature search strategy, study selection, summaries of selected studies, risk of bias, study quality assessment for included studies, and reasons for excluded studies are provided in the Supplementary material (Supplementary Tables S1–S40).

Questions

QUESTION #1: Do rapid microbiological diagnostics impact on the management and clinical outcome of critically ill/septic patients?

Recommendation 1.1:

In critically ill patients, the use of rapid diagnostic microbiological tests (RDTs) should be adopted since they have the potential to improve the timing to initiate appropriate therapy and possibly improve the patient outcome.

Strength of recommendations: **STRONG** Certainty of evidence: **LOW**

Rationale: Sepsis affects a large proportion of the critically ill population. Current guidelines recommend starting antibiotic therapy preferably within the first hour for adults with possible septic shock or a high likelihood of sepsis [19], because a delay could result in decreased survival. However, the current standard of care depends on blood culture-based diagnosis and often takes at least 48–72 h to produce results. Therefore, rapid diagnosis of severe infection or sepsis is crucial to improving the management of critically ill patients. Rapid phenotypic and molecular techniques improve the timeliness of administration of appropriate antibiotic therapy [11,12], and the use of molecular methods results in rapid de-escalation of the antibiotic in septic patients compared with conventional blood cultures. Several types of RDTs are available: some RDTs only identify pathogens but not the resistance profile, while other RDTs might detect specific resistance genes (such as *mecA*, *bla_{KPC}*, *bla_{NDM}*). In critically ill settings, the use of molecular RDTs may impact on the clinical outcome of patients. Of note, a recent study showed that the use of *bla_{KPC}* PCR testing on pos-

itive blood cultures is associated with decreased time to appropriate therapy and decreased mortality for CRE bacteraemia [20]. This study has peculiar importance because, despite its observational design, it was conducted in eight New York and New Jersey medical centres and reflects the importance of molecular methods in the context of high prevalence of KPC-producing CRE [20]. The authors showed that the use of PCR testing on blood cultures led to earlier initiation of active therapy and, consequently, to a reduction in the mortality rate among patients with CRE bacteraemia. Thus, implementation of such assays with more intense, real-time antimicrobial stewardship may further improve time to appropriate therapy and de-escalation of broad-spectrum therapy [21]. Although this approach generally does not directly affect mortality, it is likely to be a safe strategy in septic patients that avoids unnecessary exposure to antimicrobials, adverse events and the development of further antibiotic resistances [21,22].

Recommendation 1.2:

Rapid molecular identification of micro-organisms from blood cultures as well as rapid detection of their resistance mechanisms should be carefully integrated in the laboratory workflow scheme. These tests may be useful tools for 24 hour/day monitored care.

Strength of recommendation: **STRONG** Certainty of evidence: **MODERATE**

Rationale: Molecular identification of micro-organisms from blood cultures and their resistance mechanisms have been valorised for their easy use and short time to results [23]. However, the timing of results depends on how the test is integrated in the laboratory workflow scheme. This real-time approach may be useful for critically ill patients monitored around the clock. Rapid molecular tests associated with rapid communication are useful if aimed at patients in intensive care units (ICUs) where rapid communication leads the clinician to set up an immediate adjustment of antibiotic treatment in accordance with local guidelines and laboratory indications. Verroken et al. evaluated the role of a molecular RDT (BioFire FilmArray Blood Culture Identification Panel) designed to identify 24 micro-organisms and three antimicrobial resistance genes (*mecA*, *vanA/B* and *bla_{KPC}*) in 1 h 5 min directly from blood of positive culture bottles. The authors showed that the median time of administration of optimal antibiotic therapy in patients with bloodstream infections (BSIs) was 4.7 h using a rapid molecular method compared with 14.7 h using a rapid phenotypic method, and that these results improved the therapeutic management of 31 of 110 patients studied [24].

Recommendation 1.3:

In patients colonised or potentially infected with extended-spectrum β -lactamase (ESBL)-producing and/or carbapenem-resistant Enterobacterales (CRE), the use of molecular tests should be adopted since it is associated with a more rapid administration of appropriate antimicrobial therapy and can lead to a reduction in mortality.

Strength of recommendation: **STRONG** Certainty of evidence: **LOW**

Rationale: Patients who develop BSIs caused by antibiotic-resistant bacteria, including ESBL-producing or carbapenem-resistant enterobacteria, have limited treatment options and consequently are at greater risk of mortality, complications and prolonged hospitalisation. For Gram-negative pathogens, especially ESBL-producers or CRE, integration of rapid diagnostics with antimicrobial stewardship dramatically reduces the time to identification and leads to a faster administration of appropriate antibiotic therapy compared with conventional methods. This contributes to a reduction in mortality in settings with a high MDRO prevalence [25]. Walker et al. conducted a retrospective study showing that 30-day mortality was significantly lower after introduction of rapid testing (8.1% vs. 19.2%); however, the intervention did not affect

30-day mortality among patients admitted to the ICU [26]. This may be due to other factors that can influence correct assessment of the outcome, e.g. the rate of drug-resistant organisms, choice of empirical antibiotic therapy, and antibiotic stewardship practices that may differ by institution. GRADE for recommendations 1.1–1.3 are reported in Table 1.

QUESTION #2: Do rapid microbiological diagnostics favour the adjustment of empirical therapy and the transition to targeted therapy?

Recommendation 2.1:

In hospitalised patients, the use of rapid diagnostic tests (RDTs) is recommended to improve time to initiate appropriate antimicrobial therapy.

Strength of recommendation: **STRONG** Certainty of evidence: **LOW**

Rationale: The use of empirical antibiotic therapy is recommended in the presence of severe infections, pending microbiological results. Generally, the choice of antibiotic and the duration of therapy should be based on the identification of the pathogenic micro-organism, the type of patient care, local epidemiology and ASPs.

The availability of RDTs [matrix-assisted laser desorption/ionisation time-of-flight (MALDI-TOF)] has significantly reduced the time to pathogen identification compared with conventional testing, resulting in a significant improvement in response times [27–29]. Table 2 summarises the differences in identification times between rapid microbiological testing and routine methods as reported in the studies analysed. This approach, integrated into an ASP [30] and supported by an extended laboratory workflow operating with a 24-h/7-day model [31], could improve the adjustment of empirical therapy and reduce the time to appropriate targeted therapy.

Recommendation 2.2:

Rapid diagnostic tests (RDTs) are recommended for improving time to effective therapy in bloodstream infections (BSIs) caused by resistant organisms, particularly vancomycin-resistant enterococci (VRE), methicillin-resistant Staphylococcus aureus (MRSA), multidrug-resistant Pseudomonas aeruginosa, and extended-spectrum β -lactamase (ESBL)- and carbapenemase-producing Enterobacterales.

Strength of recommendation: **STRONG** Certainty of evidence: **LOW**

Rationale: Rapid tests for the identification of micro-organisms have emerged in the last decade, including MALDI-TOF and rapid multiplexed PCR panels, with turnaround times of 1–5 h; however, standard phenotypic antimicrobial susceptibility testing (AST) requires 2–4 days, considering the time required for subculturing and AST. Recently, rapid phenotypic and genotypic tests have been developed that reduce the time required to perform AST for some resistance mechanisms, thereby reducing the time to initiation of appropriate antibiotics. Due to technical limitations and the complexity of resistance mechanisms, they do not fully cover the antimicrobial resistance profile found especially in Gram-negative rods. Beuving et al. reported that empirical antimicrobial therapy was inappropriate in 26% of all patients, that this was more common with nosocomial bacteraemia than with community-acquired infections, and that rapid identification and rapid AST in BSIs reduces the time to initiation of targeted antibiotic therapy by ≥ 15.6 h compared with conventional testing [32].

Rapid identification is expected to have a large positive impact in settings that have time-consuming AST methods in place and high rates of resistant Gram-negative pathogens, but might have a limited impact in hospital with low antibiotic resistance rates [33], where fewer patients receive unnecessary broad-spectrum empirical combination therapies. Fully automated PCR-based tests, which

Table 1
GRADE table for recommendations 1.1–1.3 and 2.1–2.4.

Recommendation	No. of studies	Study design	Risk of bias ^a	Inconsistency	Indirectness	Imprecision	Other considerations	Certainty of evidence
1.1–1.3	8 [11,12,21–26]	One meta-analysis (including 4 RCTs, 11 pre/post-intervention studies and 1 retrospective study). One RCT. Five quasi-experimental studies. One observational study	Serious risk of bias due to confounding (unmeasurable factors, and chronologic, information and reporting bias)	No serious inconsistency (fairly consistent direction of effect for all outcomes)	Serious indirectness (mixed population of ICU patients and non-ICU; secondary outcome)	Serious imprecision due to small sample sizes in some studies	No serious risk of publication bias	Moderate/low (consistent direction of effect for time to appropriate therapy, but conflicting evidence for mortality ^b)
2.1–2.4	10 [27–36]	One meta-analysis (including 2 RCTs, 26 pre/post-intervention studies and 3 case-control studies). Three RCTs. Two non-randomised controlled CTs. Two quasi-experimental studies. Two observational studies	Serious risk of bias due to confounding (unmeasurable factors, and chronologic, information, working hours and reporting bias)	Serious inconsistency (no consistent direction of effect for all outcomes)	Serious indirectness (different setting; indirect comparison of intervention and control groups; secondary outcome)	Serious imprecision due to small sample sizes in some studies	No serious risk of publication bias	Low (inconsistent direction of effect for time to appropriate therapy)

RCT, randomised controlled trial; ICU, intensive care unit; CT, clinical trial.

^a For observational studies, risk of bias was assessed through the Newcastle–Ottawa Scale (NOS) [17], whereas for RCTs risk of bias was assessed through the Effective Practice and Organisation of Care guidelines [16]. High risk of bias converted to 'very serious risk of bias', low risk of bias converted to 'no serious risk of bias', whereas moderate/unclear risk of bias converted to 'serious risk of bias' or 'no serious risk of bias' according to evaluator judgement. The quality assessment of the included systematic reviews and meta-analyses was determined by the US National Institutes of Health tool [15].

^b Heterogeneous assessment of mortality.

Table 2

Difference in response times between molecular and phenotypic methods compared with conventional methods analysed in the included studies.

Method	Intervention	Comparator MALDI-TOF	Routine culture	Type of study	
Molecular methods	Film array (24/7) 1 h 35	MALDI-TOF (once a day) 14 h 41		Pre/post-intervention study [24]	
	Verigene (24/7) 10.9 h		37.9 h (once a day)	Retrospective study [26]	
	Film array (24/7) 1.3 h		51 h (not 24/7)	Pre-post quasi-experimental study [23]	
	Verigene (24/7) 21.7 h		80.8 h (24/7)	Pre/post-intervention study [31]	
	Multiplex PCR assay (24/7) 50.7 h		66.3 h (24/7)	RCT [32]	
	Film array (24/7) 1.3 h	MALDI-TOF standard 22 h		Prospective RCT [36]	
	Phenotypic methods	MALDI-TOF (not 24/7) 36.6 h		77.7 h (not 24/7)	Pre-post quasi-experimental study [12]
		MALDI-TOF (24/7) 14.5 h		40.9 h	Pre/post-intervention study [25]
		MALDI-TOF standard 2.37 days		3.27 days	Retrospective study [27]
		MALDI-TOF short incubation 1.72 days			
MALDI-TOF standard 34.58 h			48.91 h	Retrospective study [28]	
MALDI-TOF directly on BC+ 30.1 h		MALDI-TOF standard 59.1 h		Clinical controlled trial [35]	
Direct VITEK®2 + MALDI-TOF (24/7) 12.3–16.3 h		MALDI-TOF and MicroScan from rapid subculture 24.1–25.8 h		Pre-post quasi-experimental study [30]	
MALDI-TOF after extraction with conventional method 38.5 h			55.2 h	RCT [29]	
MALDI-TOF + rapid AST in dd 23 h/23 h		MALDI-TOF + rapid AST in dd 22.8 h/21.8 h		Pre-post quasi-experimental study [33]	
Rapid ADX 2.2 h/7.4 h					
MALDI-TOF short incubation 21.3 h		47.5 h	RCT [37]		

MALDI-TOF, matrix-assisted laser desorption/ionisation time-of-flight; RCT, randomised controlled trial; BC+, positive blood culture; AST, antimicrobial susceptibility testing; ADX, Accelerate Pheno® System.

provide result in <1 h, have been developed in recent years and allow rapid detection and differentiation of five genes (*bla_{KPC}*, *bla_{VIM}*, *bla_{IMP-1}*, *bla_{NDM}* and *bla_{OXA-48}* and variants) responsible for carbapenem resistance in Enterobacterales. These RDTs are generally used to detect faecal colonisation for surveillance and screening purposes, with excellent sensitivity and specificity, and are also validated for polymicrobial specimens such as abdominal drainage fluid and bronchial specimens. Use of molecular assays for the detection of carbapenemases or *mecA* genes directly on positive blood cultures showed good sensitivity and may substantially improve the time from blood culture collection to the start of appropriate antibiotic therapy [20,29,31].

Recommendation 2.3:

The implementation of rapid diagnostic tests (RDTs) should include activation of an antimicrobial stewardship programme (ASP) (including an action plan to ensure correct interpretation, real-time reporting and guidance on optimal therapy).

Strength of recommendation: **STRONG** Certainty of evidence: **MODERATE**

Rationale: Antimicrobial prescribing is a complex process influenced by multiple variables in addition to the time required to obtain AST results, including the availability of expert clinical advice (e.g. antimicrobial stewardship teams), therapeutic inertia, potential adverse drug effects, and a number of patient factors such as clinical status, drug allergies, immunocompetence (clinicians are often reluctant to de-escalate antibiotic therapy in neutropenic patients with bacteraemia) [34].

Osthoff et al. showed that an ASP that provides step-by-step guidance to clinicians, starting from Gram staining results to pathogen identification and susceptibility testing, increased the proportion of patients receiving active treatment from 62.5% before availability of Gram staining to 90.6% before conventional identification, demonstrating the importance of activating an ASP [35].

Thus, understanding the role of these variables in facilitating improved outcomes with rapid direct AST may be essential for justifying its clinical implementation.

To define best practices, additional studies are needed to assess the effect of rapid AST in the community hospital setting and to assess the benefits of various microbiological technologies in combination with an ASP.

Recommendation 2.4:

The use of rapid diagnostic tests (RDTs) is recommended since it can lead to a more judicious use of antibiotics; it should be part of the standard of care in patients with bloodstream infections (BSIs).

Strength of recommendation: **CONDITIONAL** Certainty of evidence: **LOW**

Rationale: RDTs can increase the use of narrow-spectrum antibiotics, reduce the use of antibiotics for contaminants, facilitate rapid antibiotic escalation and reduce the emergence of antibiotic resistance. Results from a prospective RCT reveal that the time from Gram staining to appropriate antimicrobial escalation/de-escalation was shorter in the rapid AST group compared with the control group. Rapid identification and rapid AST directly from blood cultures implemented with templated comments or antimicrobial stewardship oversight can optimise the prescription of an

tibiotic therapy [36]. GRADE for recommendations 2.1–2.4 are reported in Table 1.

QUESTION #3: Does rapid microbial identification reduce the duration of therapy and the length of stay (LOS) in infections caused by multidrug-resistant bacteria?

Recommendation 3.1:

In hospitalised patients, the use of rapid diagnostic methods is suggested to decrease hospital length of stay (LOS), improving the outcome of patients requiring a change in therapy.

Strength of recommendation: **CONDITIONAL** Certainty of evidence: **LOW**

Rationale: Based on overall strength of evidence for the effectiveness of rapid diagnostic and identification methods, multiple improvements in patient outcomes were noted, including reductions in hospital LOS and antibiotic use. Data suggest that rapid diagnostic methods have the potential to reduce the time to targeted therapy and possibly improve patient outcomes. Integration of rapid identification and susceptibility techniques with ASPs significantly reduced the time to optimal therapy and decreased hospital LOS. A recent meta-analysis of 16 studies provided a comprehensive and updated assessment of the effect of molecular rapid diagnostic testing (mRDT) on time to effective therapy and LOS compared with conventional microbiology methods in patients with BSIs [34]. mRDT methods included PCR, MALDI-TOF mass spectrometry and peptide nucleic acid fluorescent in situ hybridisation (PNA-FISH). PCR or other microarray technologies were used most frequently (64.5%), followed by PNA-FISH (19.4%) and MALDI-TOF analysis (12.9%). LOS was significantly shorter with mRDT [−2.48 days; 95% confidence interval (CI) −3.90 to −1.06 days] [34].

RDTs have significantly reduced the time to pathogen identification compared with conventional tests, resulting in a significant shortening of response times. This result was demonstrated in a retrospective study by Delpont et al. that showed improved outcomes in those patients requiring a change in their antibiotic compared with patients whose empirical therapy was considered optimal. This improvement was associated with a reduction in LOS from 4.72 days ($P < 0.031$) to 1.77 days ($P < 0.71$) and an associated reduction in the absolute mortality risk of 3.79% [27].

Finally, a RCT showed that implementation of rapid microbial identification by MALDI-TOF testing of microcolonies (after 4–6 h of incubation) rather than on an extract from blood culture decreased the median time to identification from 47.5 h to 21.3 h ($P < 0.001$). After establishment of this technique, the median LOS decreased from 10.83 days to 9.79 days ($P = 0.016$), the rate of ICU transfer decreased from 13.8% to 11.6% ($P = 0.054$) and the mortality rate decreased from 20.9% to 18.3% ($P = 0.047$) [37].

Recommendation 3.2:

Implementing molecular rapid diagnostic testing (mRDT) with an antimicrobial stewardship programme (ASP) can reduce time to effective therapy and length of stay (LOS) in patients with bloodstream infections (BSIs) caused by multidrug-resistant bacteria. Effectiveness was demonstrated in a 24-h/7-day laboratory organisation.

Strength of recommendation: **STRONG** Certainty of evidence: **LOW**

Rationale: Molecular blood culture testing has been valorised for its ease of use and short time to results; however, this time interval rarely reflects the time to identification as it depends on how the test is integrated in the laboratory workflow scheme. Use of a phenotypic rapid method for AST (Accelerate Pheno® System; Accelerate Diagnostics Inc.) compared with conventional diagnostics and with ASP interventions significantly decreased the time from Gram stain to identification (median, 23 h vs. 2.2 h; $P < 0.001$), to AST (median, 23 h vs. 7.4 h; $P < 0.001$) and to optimal therapy (median, 11 h vs. 7 h; $P = 0.024$), reducing the

time to appropriate antimicrobial therapy (median, 27.8 h vs. 12 h; $P = 0.019$); this approach also decreased LOS and improved patient outcomes [33].

In a prospective RCT, the time from Gram staining to appropriate antimicrobial de-escalation/escalation was shorter in the rapid diagnostics compared with the control group. Rapid identification with a syndromic test (FilmArray™ Blood Culture Identification Panel; bioMérieux Diagnostics) and rapid susceptibility testing directly from blood culture, implemented with an ASP, was able to optimise antibiotic prescription. Furthermore, there were no differences in mortality or LOS between the groups with and without input from an ASP (24/7). A possible explanation can be attributed to differences in study designs and/or to the fact that 70% of study subjects were already receiving at least one active agent at enrolment and were generally being overtreated rather than undertreated [36].

The real-time approach is useful for critically ill patients undergoing continuous monitoring but could lack clinical responsiveness overnight in non-critical hospital units. Rapid molecular tests associated with rapid communication are useful if aimed at patients in ICUs, where rapid communication leads to an immediate adjustment of antibiotic treatment in accordance with local guidelines and laboratory indications [34]. GRADE for recommendations 3.1 and 3.2 are reported in Table 3.

QUESTION #4: Does knowledge of local/regional/national epidemiology favour the implementation of rational empirical therapy?

Recommendation 4.1:

Updated local antibiograms with pathogen-specific susceptibility data should be produced at least annually together with data on antimicrobial use to optimise expert-based recommendations for empirical therapy. First evidence of the importance of the preliminary report.

Strength of recommendation: **STRONG** Certainty of evidence: **MODERATE**

Rationale: Few studies have evaluated the importance of epidemiology to the implementation of a rational empirical therapy in hospitalised patients. Rodriguez-Maresca et al. developed and implemented a computer application based on local bacterial susceptibility to antibiotics, with the aim of evaluating the most appropriate antibiotic treatment for ICU patients with suspected nosocomial infections [38]. Empirical antibiotic treatment was implemented in 173 (79.4%) of 218 patients in the study, while local resistance map (LRM) guidelines were followed in only 44 (25.4%) of these. Empirical antibiotic treatment appropriateness was significantly higher when LRM guidelines were followed ($P = 0.005$). Among the 92 patients for whom an antibiogram of the isolated micro-organism was available, 77 were treated according to clinical criteria and 36.4% of the antibiotics prescribed in this group were active against the subsequently isolated bacteria, compared with 80% of the 15 patients treated according to LRM guidelines [38]. In this study, preliminary microbiological reports (PMRs) with therapeutic recommendations were followed in 68 (70.8%) of the 96 patients for whom they were issued, resulting in maintenance of initial empirical treatment in 4 patients (5.9%), modification in 36 patients (52.9%) and prescribing treatment in 28 previously untreated patients (41.2%). Overall, 82.4% of prescriptions based on PMR therapeutic recommendations were clinically successful ($P = 0.001$) [38]. Parameters such as mortality (20% vs. 27%; $P = 0.75$), ICU LOS (13.8 days vs. 19.5 days; $P = 0.16$) and antibiotic appropriateness (80% vs. 26%; $P = 0.05$) were also improved [38]. In all studies included [39–41], computerised tools providing time series analyses of AMR surveillance together with antimicrobial consumption data helped AMR surveillance teams to provide useful support for clinical decisions. The analysis of trends and the effect of antimicro-

Table 3
GRADE table for recommendations 3.1 and 3.2.

No. of studies	Study design	Risk of bias ^a	Inconsistency	Indirectness	Imprecision	Other considerations	Certainty of evidence
4 [27,33,34,37]	Retrospective cohort study Retrospective review Systematic review and meta-analysis Observational study	Serious risk of bias due to confounding	No serious inconsistency No serious inconsistency	Serious indirectness due to mixed population in one study (VRE and non-VRE) Serious indirectness	No serious imprecision Serious imprecision	No serious risk of publication bias Serious risk of publication bias	Moderate
1 [36]	RCT	Serious risk of bias (random sequence generation and allocation concealment 'high risk')	Serious inconsistency	Serious indirectness (not consistent direction of effect for length of stay/duration of treatment)	Serious imprecision due to the limited sample size	No serious risk of publication bias	Low

VRE, vancomycin-resistant enterococci; RCT, randomised controlled trial.

^a For observational studies, risk of bias was assessed through the Newcastle–Ottawa Scale (NOS) [17]. For RCTs, risk of bias was appraised through the Effective Practice and Organisation of Care guidelines [16]. High risk of bias converted to 'very serious risk of bias', low risk of bias converted to "no serious risk of bias", whereas moderate/unclear risk of bias converted to 'serious risk of bias' or 'no serious risk of bias' according to evaluator judgement.

Table 4
GRADE table for recommendation 4.1.

No. of studies	Study design	Risk of bias ^a	Inconsistency	Indirectness	Imprecision	Other considerations	Certainty of evidence
1 [36]	Prospective quasi-experimental study	Serious risk of bias due to confounding	No serious inconsistency	Serious indirectness (patients were not managed with a specific protocol and it was therefore not possible to control for all relevant clinical variables)	Serious imprecision due to small sample sizes	No serious risk of publication bias	Low
1 [41]	Systematic review	Serious risk of bias due to confounding	Serious inconsistency owing to different outcomes assessed	Serious indirectness due to mixed population	No serious imprecision	No serious risk of publication bias	Moderate
2 [39,40]	Controlled before–after study (2008–2012) Interrupted time series (2014 vs. 2015)	Serious risk of bias (random sequence generation and allocation concealment 'High risk') Low risk of bias	No serious inconsistency No serious inconsistency	No serious indirectness No serious indirectness	Serious imprecision due to small sample sizes in many studies Serious imprecision due to small sample sizes in many studies	No serious risk of publication bias	Moderate

^a For observational studies, risk of bias was assessed through the Newcastle–Ottawa Scale (NOS) [17]. For randomised controlled trials, risk of bias was appraised through the Effective Practice and Organisation of Care guidelines [16]. High risk of bias converted to 'very serious risk of bias', low risk of bias converted to 'no serious risk of bias', whereas moderate/unclear risk of bias converted to 'serious risk of bias' or 'no serious risk of bias' according to evaluator judgement.

bial usage can be used to forecast variations in AMR and to select the appropriate therapeutic regimen accordingly. GRADE for recommendation 4.1 is reported in Table 4.

QUESTION #5: What is the treatment of choice for carbapenem-resistant Enterobacteriales (CRE) infections?

Recommendation 5.1:

In patients with infections caused by carbapenem-resistant Enterobacteriales (CRE), rapid testing should be used to identify specific carbapenemase families (e.g. KPC, NDM, VIM, OXA-48-like). Clinicians should adopt different treatment strategies based on the type of causative carbapenemase-producing Enterobacteriales (CPE).

Strength of recommendation: **STRONG** Certainty of evidence: **MODERATE**

Rationale: CRE represent a serious public-health threat worldwide. Epidemiological data from the EARS-Net 2019 surveillance

report highlights considerable heterogeneity in the prevalence of CRE across EU/EEA countries [4]. However, most countries reported carbapenem resistance in *K. pneumoniae* of >10% and some (including Italy and Greece) of >50% [4]. Remarkably, carbapenem resistance has increased more than seven-fold since 2006 and for several individual EU/EEA countries, most notably in South and South Central Europe, the increase has been substantially larger [42].

CRE include pathogens with multiple mechanisms of resistance. The most common mechanism that confers resistance to carbapenems in Enterobacteriales is the production of carbapenemase enzymes and, therefore, the terminology 'carbapenemase-producing Enterobacteriales' (CPE) may be considered more precise than 'CRE' [43]. Other less frequent mechanisms (e.g. porin loss) may be responsible for carbapenem resistance among CRE that are not classified as CPE. Among the four classes of β -lactamases defined by

the Ambler classification system, the carbapenemases that confer carbapenem resistance in Enterobacteriaceae belong to Class A [*K. pneumoniae* carbapenemase (KPC)], Class B [metallo- β -lactamases (MBLs): NDM, VIM, IMP] and Class D (OXA-48-like) [44].

Although KPC remains the most common carbapenemase [45], increasing detection of non KPC-producing CRE has been reported worldwide [46–48]. In a recent multicentre surveillance study, the majority of meropenem-non-susceptible Enterobacterales carried KPC-type carbapenemases (47.4%), followed by MBLs (20.6%) and OXA-48-like β -lactamases (19.0%) [48]. Knowledge of the molecular mechanism responsible for the carbapenem-resistant phenotype is crucial because each class of enzymes confers variable susceptibility profiles that require different treatment strategies. MBLs are particularly worrisome due to their ability to hydrolyse all classes of β -lactams, except monobactams (aztreonam), as well as the inability of the classic serine β -lactamase inhibitors to inhibit them owing to the co-production of several ESBLs [49,50]. Because time from blood culture collection to the start of active antibiotic therapy influences the outcome of critically ill patients with BSI caused by KPC-producing *K. pneumoniae* [9], rapid testing on blood or other isolates may be crucial for starting active antibiotic therapy early and applying treatment approaches based on the specific carbapenemase. Thus, we strongly recommend the use of rapid testing strategies to identify specific carbapenemases and to guide antibiotic therapy.

Recommendation 5.2:

2.a In patients with infections caused by KPC-producing carbapenem-resistant Enterobacterales (CRE), novel β -lactam agents such as ceftazidime/avibactam and meropenem/vaborbactam should be the first-line treatment options.

2.b Imipenem/relebactam and cefiderocol may also be considered.

2.a	Strength of recommendation:	STRONG	Certainty of evidence:	MODERATE
2.b	Strength of recommendation:	CONDITIONAL	Certainty of evidence:	LOW

Rationale: Before the introduction of new antibiotics, combinations of traditional antibiotics were used to treat KPC-producing *K. pneumoniae* infections, but there was no consensus on the most effective regimens [51–53]. Strategies such as high-dose carbapenems in combination regimens, a double carbapenem strategy, and best combination regimens were debated. Moreover, there were concerns regarding poor efficacy and unfavourable toxicity profiles with traditional antibiotic regimens, which often included colistin. Remarkably, a systematic review and meta-analysis of 54 studies involving 3352 patients with carbapenem-resistant *K. pneumoniae* infections treated with traditional antibiotics found that approximately one in three patients died and <70% achieved a clinical or microbiological response [53]. The introduction of new antibiotics changed the therapeutic approach to these infections and improved clinical outcomes in patients with CRE infections.

RCTs in patients with CRE infections are lacking, therefore the recommendations from this panel are based mainly on observational studies, with a corresponding moderate or low certainty of evidence (Table 5). Nevertheless, a growing body of evidence from real-world experience highlights the benefit of new antibiotics against KPC over traditional antibiotic regimens in terms of clinical efficacy and safety. Although no RCTs on the efficacy of ceftazidime/avibactam are available in this setting, its use in patients with KPC-producing CRE infections is supported by favourable results of several observational studies [53–59]. Among patients with BSI caused by KPC-producing *K. pneumoniae*, the rate of 30-day clinical success was significantly higher among patients treated with ceftazidime/avibactam compared with those who received a carbapenem plus either an aminoglycoside ($P = 0.04$) or colistin ($P = 0.009$), or those who received other regimens ($P = 0.004$)

[55]. Other large observational studies confirmed these findings [56,58]. In a recent multicentre prospective national registry, 71 patients with KPC-producing *K. pneumoniae* BSI treated with ceftazidime/avibactam were propensity score-matched with a cohort of 71 patients treated with *in vitro* active agents other than ceftazidime/avibactam [59]. The 28-day mortality was significantly lower in patients who received ceftazidime/avibactam (18.3% vs. 40.8%; $P = 0.005$) [59]. Ceftazidime/avibactam was shown to be safer than colistin because of its lower risk of nephrotoxicity [9,56], and it had a higher clinical cure rate compared with other drugs in a small observational study of haematology patients with CPE infections [54].

Real-world experience with meropenem/vaborbactam is limited because of its recent introduction; however, in the phase 3 TANGO II study, meropenem/vaborbactam monotherapy for CRE infection was associated with a higher clinical cure rate, decreased mortality and reduced nephrotoxicity compared with the best available therapy (BAT), which consisted of monotherapy or combination therapy with polymyxins, carbapenems, aminoglycosides and tigecycline or of ceftazidime/avibactam alone [60].

In a retrospective study, clinical success rates were similar in patients with CRE infections treated with ceftazidime/avibactam or meropenem/vaborbactam [61]. Currently, there is insufficient evidence to prefer one of these agents over the other and more evidence is needed to guide their use in different patient categories and infection types according to their pharmacokinetic/pharmacodynamic (PK/PD) properties. Based on current evidence, we strongly recommend the use of either ceftazidime/avibactam or meropenem/vaborbactam in patients with infections caused by KPC-producing CRE. However, the site of infection should be considered. Meropenem and vaborbactam achieve similar epithelial lining fluid (ELF) concentrations, with intrapulmonary penetration ratios from plasma of 63% for meropenem and 65% for vaborbactam. Importantly, the ELF concentrations of meropenem and vaborbactam remain consistently several fold higher than the MIC₉₀ (minimum inhibitory concentration inhibiting the growth of 90% of isolates) of KPC-producing *K. pneumoniae* [62], suggesting that meropenem/vaborbactam may be considered as the first choice in specific types of infections, such as pneumonia. Local epidemiology and the emergence of ceftazidime/avibactam resistance in KPC-producing isolates (that range from 0% to 12.8%) should be also considered [54,63,64]. KPC variants (e.g. mutations in the *bla*_{KPC-3} gene, D179Y variants) that confer resistance to ceftazidime/avibactam have been described [65]; in this situation, meropenem/vaborbactam may be a therapeutic option [66].

Based on data from *in vitro* studies, imipenem/relebactam and cefiderocol may also be considered in patients with KPC-producing CRE infections. However, clinical studies of their efficacy in these patients are not available. KPC infections accounted for a minority of cases in the study population of the CREDIBLE-CR and RESTORE-IMI trials [67,68]. We recommend the use of imipenem/relebactam or cefiderocol as *potential* alternatives for the treatment of infections involving KPC-producing CRE.

Recommendation 5.3:

In patients with infections caused by OXA-48-like producing carbapenem-resistant Enterobacterales (CRE), ceftazidime/avibactam should be the first-line treatment option.

Strength of recommendation:	CONDITIONAL	Certainty of evidence:	VERY LOW
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Rationale: Very limited clinical data are available on the treatment of infections due to OXA-48-producing CRE. Data about the role of ceftazidime/avibactam come from observational studies with small sample sizes [69,70]. Ceftazidime/avibactam showed

Table 5

Quality of studies about antibiotic treatment of infections caused by carbapenem-resistant Enterobacterales (CRE) (recommended for all acute-care hospitals).

Antibiotic treatment by organism	Quality of studies			Overall certainty of evidence
	Moderate	Low	Very low	
KPC-producing CRE				
CZA or MVB	[9,55–60]	[54,61]	–	Moderate
I-R or FDC	–	[67] ^a	–	Low
OXA-48-like-producing CRE				
CZA	–	–	[70]	Very low
MBL-producing CRE				
CZA plus ATM	[72]	–	–	Low
FDC	–	[67] ^a	–	Low
Combination vs. monotherapy (for CZA)	[76]	[75]	–	Insufficient (best practice recommendation)

CZA, ceftazidime/avibactam; MVB: meropenem/vaborbactam; I-R, imipenem/relebactam; FDC, cefiderocol; MBL, metallo- β -lactamase; ATM, aztreonam.

^a Evidence from the CREDIBLE-CR study comes from a subgroup of few patients with CRE infections. Thus, the quality of the study was judged as low, considering imprecision (small sample size of patients with CRE infections) and potential imbalance between cases and controls in this subgroup of patients.

promising results in only one comparative study in which OXA-48 was the predominant carbapenemase in patients with severe CRE infections [70]. Further observational studies are needed to explore the efficacy of ceftazidime/avibactam or other new antibiotics in this patient category.

Recommendation 5.4:

4.a In patients with infections caused by metallo- β -lactamase (MBL)-producing carbapenem-resistant Enterobacterales (CRE), ceftazidime/avibactam plus aztreonam should be preferred.

4.b Cefiderocol may also be considered.

4.a	Strength of recommendation:	STRONG	Certainty of evidence:	MODERATE
4.b	Strength of recommendation:	CONDITIONAL	Certainty of evidence:	LOW

Rationale: MBL-producing Enterobacterales are endemic in the Indian subcontinent but are increasingly reported in Europe and all over the world. A large outbreak of New Delhi metallo- β -lactamase (NDM)-producing CRE was reported in the Tuscany region in Italy from November 2018 [71]. From a therapeutic point of view, MBLs can inactivate all β -lactams except aztreonam. However, aztreonam cannot be used alone because of the concomitant co-production of other enzymes (ESBLs and other cephalosporinases). Novel combinations, such as ceftazidime/avibactam and meropenem/vaborbactam, do not show in vitro activity against MBL-producing isolates [50]. Very limited studies on the optimal therapy for MBL-producing CRE infections are available. Clinical experience with the few antibiotics active in vitro (colistin, fosfomycin, tigecycline) is limited to case reports or case series. The combination of ceftazidime/avibactam plus aztreonam displayed in vitro synergy [72], and a recent observational study including patients with BSI caused by MBL-producing CRE (mainly NDM-producing *K. pneumoniae*) showed that 30-day mortality was significantly lower in patients treated who received ceftazidime/avibactam plus aztreonam compared with patients who received other antibiotics active in vitro, including colistin, tigecycline and fosfomycin (19.2% vs. 44%; $P = 0.007$) [72]. Importantly, the highest mortality rates were observed in patients who received colistin-containing regimens [72].

Cefiderocol may be an alternative option for infections caused by MBL-producing CRE. This recommendation is based on results from the RCT CREDIBLE-CR. Although not specifically conducted in patients with infections caused by MBL-producing CRE, the CREDIBLE-CR showed that in this subgroup, clinical cure was achieved by 12 (75%) of 16 patients treated with cefiderocol and 2 (29%) of 7 patients treated with BAT [67]. Thus, with difference

in the strength of recommendations, we recommend the use of the combination ceftazidime/avibactam plus aztreonam (strong) or cefiderocol (conditional) for the treatment of infections caused by MBL-producing CRE. It should be also considered that the GRADE for the development of this document has been conducted before some studies are published. Recently, Timsit et al. evaluated the efficacy of cefiderocol against MBL-producing isolates from CREDIBLE-CR and APEKS-NP and found higher rates of clinical cure (70.8%) and microbiological eradication (58.3%), and lower 28-day mortality (12.5%) in patients who received cefiderocol with respect to comparators [73]. While the development of efficient MBL inhibitors is ongoing, cefiderocol appears to be a promising therapeutic option and represents a silver lining for the treatment of MBL-producing isolates. However, some shadows in its use against MBLs (high MIC values, risk of treatment-emergent resistance and role of combination therapy) should be considered and further investigated [74].

Recommendation 5.5:

There are insufficient data supporting or against the use of ceftazidime/avibactam as combination therapy or monotherapy.

GOOD PRACTICE STATEMENT Based on the panel opinion (the available evidence was not deemed sufficient for developing a recommendation with GRADE methods)

Rationale: No conclusive data are available regarding the use of ceftazidime/avibactam as monotherapy or in combination with other drugs [75,76]. In a post-hoc analysis of a retrospective cohort study, clinical success did not differ among patients who received ceftazidime/avibactam monotherapy, ceftazidime/avibactam combination therapy and meropenem/vaborbactam monotherapy [61]. However, an increase in recurrence was observed in the ceftazidime/avibactam monotherapy group [61]. A recent study including patients with KPC-producing *K. pneumoniae* infections showed that mortality was not different between patients who received ceftazidime/avibactam as monotherapy and those treated with a combination therapy (26.1% vs. 25.0%; $P = 0.79$) [76]. Although not statistically significant, combination regimens were associated with better survival in patients with lower respiratory tract infections, especially ventilator-associated pneumonia (VAP), suggesting a potential role of combination therapy in specific types of infection [75]. GRADE for recommendations 5.1–5.4 (CRE) is reported in Table 6.

QUESTION #6: What is the therapy of choice for infections caused by *Pseudomonas aeruginosa* with difficult-to-treat resistance (DTR-PA)?

Table 6
GRADE table for recommendations 5.1–5.4.

No. of studies	Study design	Risk of bias ^a	Inconsistency	Indirectness	Imprecision	Other considerations	Certainty of evidence
17 [9,51–61,65,67,72,75,76]	2 RCTs 13 observational studies 2 systematic reviews	Serious risk of bias	No serious inconsistency	No serious indirectness	Imprecision due to small sample sizes in many studies (both in observational studies and RCTs)	No serious risk of publication bias	Moderate/low

RCT, randomised controlled trial.

^a For observational studies, risk of bias was assessed through the Newcastle–Ottawa Scale (NOS) [17], whereas for RCTs risk of bias was appraised through the Effective Practice and Organisation of Care guidelines [16]. High risk of bias converted to 'very serious risk of bias', low risk of bias converted to 'no serious risk of bias', whereas moderate/unclear risk of bias converted to 'serious risk of bias' or 'no serious risk of bias' according to evaluator judgement.

Discussion of literature search strategy: Among Gram-negative bacteria, *P. aeruginosa* has a remarkable capacity to develop resistance to commonly used antibiotics and is one of the principal healthcare-associated pathogens [77]. Carbapenem-resistant *P. aeruginosa* (CRPA) have been acknowledged as a threat of utmost importance, but this definition encompasses isolates that have simply lost the carbapenem-specific outer membrane porin D (OprD), thus compromising only carbapenems but not agents such as piperacillin/tazobactam or ceftazidime [43]. The concept of 'difficult-to-treat' resistance (DTR; defined as non-susceptibility to all first-line, high-efficacy, low-toxicity agents) was proposed to better define *P. aeruginosa* strains of public concern and to overcome inconsistencies and limited bedside applicability of the 'classic' MDR and extensively drug-resistant (XDR) categories [78]. In line with recent guidance endorsed by the Infectious Diseases Society of America (IDSA) [79], the purpose of the present document was to find evidence regarding the best therapeutic choice against DTR-PA, defined as isolates non-susceptible to all of ceftazidime, cefepime, piperacillin/tazobactam, aztreonam, imipenem/cilastatin, meropenem, levofloxacin and ciprofloxacin.

Recommendation 6.1:

In patients with invasive infections caused by Pseudomonas aeruginosa with difficult-to-treat resistance (DTR-PA), based on pre-clinical and clinical data, novel β -lactam agents such as ceftolozane/tazobactam and ceftazidime/avibactam are currently the first-line options for targeted treatment. Imipenem/cilastatin-relebactam and cefiderocol might be potential alternatives, as well as colistin-based therapy.

Strength of recommendation: **STRONG** Certainty of evidence: **MODERATE**

Recommendation 6.2:

In patients with invasive infections caused by Pseudomonas aeruginosa with difficult-to-treat resistance (DTR-PA), combination therapy should not be the routine choice but may be considered on a case-by-case basis, especially upon consultation with infectious diseases specialists. In particular, combination regimens including fosfomycin as companion agent could be considered.

Strength of recommendation: **CONDITIONAL** Certainty of evidence: **LOW**

Rationale: It is beyond the scope of the present document to discuss the empirical selection of the most appropriate antibiotic treatment for a possible infection by *P. aeruginosa*. Regardless of the empirical agent(s) chosen initially, therapy should be tailored once culture and susceptibility results are available. In the absence of a compelling indication for targeted combination therapy, monotherapy with a highly microbiologically active, antipseudomonal β -lactam is generally preferred [77]. DTR strains are resistant to meropenem, ceftazidime and piperacillin/tazobactam and therefore should be treated with ceftolozane/tazobactam or ceftazidime/avibactam, if susceptible, as also recommended in the

Spanish guidelines [80]. Indeed, these new β -lactam/ β -lactamase inhibitor (BL/BLI) combinations have emerged as the first reliable alternative to polymyxin-based therapy for DTR-PA based on several in vitro studies that have demonstrated that both drugs have good activity against large collections of MDR/XDR isolates of *P. aeruginosa*, in some cases in >90% of the strains tested, second only to colistin [81]. Issues with colistin include a narrow therapeutic window, high nephrotoxicity risk and difficulties with establishing an appropriate dosage, whereas ceftolozane/tazobactam and ceftazidime/avibactam represent major steps forward owing to their favourable safety profiles, consistent with the β -lactam class, and because they retain good activity against many DTR-PA strains [81]. Nevertheless, no RCT demonstrated inferiority of polymyxin-based therapy in this setting and there is a relative paucity of high-quality comparative studies. Certainty of evidence from the included studies on available agents for the treatment of DTR-PA infections in acute-care hospitals is reported in Table 7.

Real-life data come from a retrospective multicentre experience from the USA in which outcomes of 100 patients with MDR/XDR *P. aeruginosa* infections receiving ceftolozane/tazobactam (91% as monotherapy) were compared with those of 100 patients receiving polymyxin or aminoglycoside-based regimens (in 72% of cases in association with another drug) [82]. Although there was no significant difference in in-hospital mortality (numerically lower in the first group, 20% vs. 25%), the clinical cure rate was clearly higher in patients receiving ceftolozane/tazobactam (81% vs. 61%; $P = 0.002$), with an adjusted odds ratio (OR) for clinical success of 2.63 (95% CI, 1.31–5.30); moreover, the incidence of acute kidney injury was far lower in the ceftolozane/tazobactam arm (6% vs. 34%; $P < 0.001$) [82].

Regarding ceftazidime/avibactam, a meta-analysis of 11 observational studies on patients with carbapenem-resistant Gram-negative bacteria (CR-GNB) infections, including DTR-PA, showed no difference in mortality or microbiological cure between monotherapy and novel BL/BLI-based combination regimens based on the novel BL/BLI [83]. The limitation of this evidence synthesis is the very low number of DTR-PA infections included (only 19 monomicrobial episodes) [83].

The therapeutic armamentarium against CR-GNB has been expanded with a further BL/BLI combination combining relebactam, an active inhibitor of class A and class C β -lactamases, with imipenem (plus cilastatin), restoring the carbapenem activity against resistant strains, including AmpC-producing *P. aeruginosa* [80]. The phase 3 RESTORE-IMI trial compared this new BL/BLI with the combination of colistin plus imipenem for invasive CR-GNB infections [68]. The study was not powered for statistical inference and randomised only 47 patients, of which just 31 represented the modified microbiological intent-to-treat (mMITT) population (77% being DTR-PA), but showed encouraging results for the primary efficacy outcomes, which were similar between treatment arms. Overall response was favourable in ~70% of patients. Regarding secondary outcomes, 28-day mor-

Table 7

Certainty of evidence from the included studies on available agents for the treatment of infections by *Pseudomonas aeruginosa* with difficult-to-treat resistance (DTR-PA) in acute-care hospitals.

Recommendation	Certainty of evidence ^a				Overall certainty of evidence ^a
	Very low	Low	Moderate	High	
R1	[89,90]	[81,83,86,87]	[67,68,88]		Moderate
R2	[89,90]	[81,83,86,87]	[67,68,88]		Low

^a The overall certainty of evidence reflects a fully contextualised approach. For this reason, it is not the sum of the certainty of evidence stemming from the single studies, which may be limited only to a part of the question/s addressed by the recommendation (see the rationales for the different recommendations in the main document).

tality and adverse events were lower in patients treated with imipenem/cilastatin–relebactam [68].

Unfortunately, none of these three novel antipseudomonal BL/BLs is active against MBL-producers. Carbapenem resistance in DTR-PA strains is predominantly mediated by loss or reduction of OprD porin, overexpression of cephalosporinase AmpC and/or overexpression of efflux pumps; however, the role of carbapenemases, specifically MBLs, has become more relevant [84]. Another mechanism of concern is ESBLs with activity against ceftolozane/tazobactam and imipenem/cilastatin–relebactam, but not ceftazidime/avibactam [84]. On the contrary, none of these three drugs is active against MBL-producing isolates, for which ceftiderocol may be a useful therapeutic option. This novel β -lactam is stable against hydrolysis by all carbapenemases and is unaffected by porin channels and efflux pumps owing to its innovative mechanism of bacterial cell entry [84]. The CREDIBLE-CR study was conceived to compare ceftiderocol with BAT for CR-GNB infections [67]. Overall, 101 patients were assigned to ceftiderocol and 51 to the comparator arm, but the mMITT population comprised 80 versus 38 patients, of which 19% had DTR-PA [67]. As with the RESTORE-IMI study, this phase 3 trial was also underpowered for statistical significance, nevertheless clinical and microbiological efficacy were similar between the two arms, supporting the clinical use of ceftiderocol for CR-GNB infections in patients with limited treatment options [67].

Pending further enlargement of the therapeutic armamentarium in this context, colistin-based treatment should still be considered, at least as a salvage option or in patients with β -lactam allergy, although the limitations of colistin are well known (i.e. high nephrotoxicity risk, suboptimal concentrations in some body districts, challenging susceptibility testing) [85].

Besides the choice of specific agents, a paramount issue for DTR-PA infections is whether targeted treatment should rely on monotherapy or combination therapy. To date, there are no compelling data in favour of combination regimens. Available evidence is often conflicting: two meta-analyses that focused on resistant Gram-negative infections, including DTR-PA, yielded conflicting results regarding the effects of combination therapy versus monotherapy on mortality [86,87]. The combination of meropenem plus colistin was not beneficial in a seminal trial that compared this combination with colistin alone in 406 patients with CR-GNB infections, only 5% of which involved DTR-PA [88].

The panel supports the potential use of combination therapy on a case-by-case basis, especially with infectious diseases specialist consultation. Fosfomycin might be an important partner drug to associate with a β -lactam or colistin [89]. In a retrospective cohort in Thailand of 136 patients with XDR *P. aeruginosa* infections, monotherapy was an independent predictor of 28-day mortality (as was absence of infectious diseases specialist consultation) compared with combination therapy based mostly on fosfomycin [90].

In conclusion, in vitro data strongly oriented some therapeutic choices, but more robust clinical data, especially in light of the new definition of DTR-PA, are needed to define the best approach to infections involving this superbug.

QUESTION #7: What is the treatment of choice for carbapenem-resistant *Acinetobacter baumannii* (CRAB) infections?

Recommendation 7.1:

There are no convincing data about the optimal antibiotic therapy against carbapenem-resistant *Acinetobacter baumannii* (CRAB) infections. Consultation by infectious diseases specialists is needed in patients with CRAB infections.

Strength of recommendation: **STRONG** Certainty of evidence: **MODERATE**

Rationale: The 2019 EARS-Net surveillance report showed a wide geographic variability in resistance among *Acinetobacter* species, with the highest percentages of carbapenem resistance reported in the Baltic countries and Southern and South-Eastern Europe [4]. Thus, the European Centre for Disease Prevention and Control (ECDC) has highlighted the need for increased efforts to face this significant threat to patients and healthcare systems in all EU/EEA countries. Infections caused by CRAB are difficult to treat and associated with high rates of treatment failure and a poor prognosis. Mortality rates in CRAB infections remain particularly high in all clinical studies, approaching 70% [91]. Several antimicrobials have been studied for the treatment of CRAB infections, but a definitive consensus for the optimal treatment is lacking [88,91–98]. Until now, colistin has been considered the backbone therapy for CRAB infections. A meta-analysis of 11 studies including a total of 1052 patients with CRAB infections compared the efficacy of polymyxin-based therapy versus non-polymyxin-based regimens, revealing that polymyxin was associated with better clinical response rates [98]. Most available studies and meta-analyses have evaluated the use of colistin, either as monotherapy or in combinations [88,91–98]. Data are conflicting, with several studies reporting no differences in clinical outcome (clinical cure and mortality) between patients treated with colistin alone and those who received colistin in combination with meropenem [88,97], fosfomycin [92] or rifampicin [91], and one open-label randomized trial on ventilator-associated pneumonia (VAP) caused by CRAB reporting a significantly higher early clinical cure rate in patients treated with colistin plus high dose ampicillin/sulbactam compared to monotherapy [93]. However, there is great heterogeneity among study populations and most studies are of low or moderate quality (Table 8). Thus, data on the therapeutic superiority of colistin monotherapy versus combination therapy are inconclusive.

Another debated point is the question of the best combination regimen for CRAB infections [94]. Although a recent network meta-analysis showed that the combination of colistin, sulbactam and tigecycline is associated with higher proportion of clinical cure and increased microbiological success, clinical studies comparing the antimicrobial treatments of such infections are inconsistent owing to small sample sizes and substantial heterogeneity among studies [94]. Moreover, most studies have serious risk of bias, with selection and confounding as the main domains affected.

In conclusion, to date there is no consensus based on strong evidence to confirm the therapeutic superiority of monotherapy

Table 8
Quality of studies about antibiotic treatment of infections caused by carbapenem-resistant *Acinetobacter baumannii* (CRAB) (recommended for all acute-care hospitals).

Antibiotic treatment for CRAB	Quality of studies			Overall certainty of evidence
	Moderate	Low	Very low	
Colistin-containing regimens FDC	[88,94–96,98]	[91–93,97] [67 ^a]	[99]	Moderate Low

FDC, cefiderocol.

^a Although it is a randomised controlled trial, using the GRADE assessment system, the analysis concluded that the CREDIBLE-CR study was of low quality with a high risk of bias because of high risk of heterogeneity between the study group in the specific subset of patients with CRAB infections.

or combination therapy or to indicate the best combination regimen. The choice of one specific combination regimen is critical and depends on the type of patient, severity of illness and type of infection (e.g. BSI, VAP). The use of recently approved cefiderocol [67,99] should be appropriately evaluated to prevent the emergence of resistant isolates.

Infectious diseases consultation was associated with reductions in 30-day and 1-year all-cause mortality for several MDR pathogens, but this was not the case for CRAB infections [100], although the study included a small number of patients with CRAB infections and may be underpowered to detect a mortality difference in this specific category.

Considering the high heterogeneity of patients with CRAB infections and the contrasting low-quality of the available data, we strongly recommend a consultation by specialists in all patients with CRAB infections.

Recommendation 7.2:

In patients who received colistin-containing regimens, kidney function should be strictly monitored because of the high risk of nephrotoxicity.

Strength of recommendation: **STRONG** Certainty of evidence: **MODERATE**

Rationale: The use of colistin is associated with two major limitations: dosing controversies pertaining to PK/PD optimisation; and adverse effects, particularly nephrotoxicity. In clinical studies, nephrotoxicity occurred in 20–60% of patients [88,91–98]. The high variability in reported nephrotoxicity rates may be due to several factors, including non-uniform definitions of nephrotoxicity, differences in severity of illness, presence of potential confounders (such as concomitant use of other nephrotoxic agents) and dosing inconsistencies [101]. A recent meta-analysis including only RCTs reported that colistin is associated with a nephrotoxicity rate of 36.2% and a 140% increase in the risk of nephrotoxicity compared with β -lactam-based regimens [102]. Moreover, colistin dosing is likely to impact the occurrence of nephrotoxicity. Weight-based dose adjustment of polymyxin B is the dosing strategy approved by the US Food and Drug Administration (FDA). However, a recent pharmacokinetic study showed that the strategy based on total body weight alone may not lead to optimal drug exposures. Instead, dosing should be selected according to the specific patient population and in conjunction with considerations about the likelihood of nephrotoxicity from a given dosing regimen [103]. This goal may be obtained using a population-specific pharmacokinetic model that, however, is not always feasible in clinical practice.

In conclusion, we strongly recommend strict monitoring of renal function when colistin is administered. Important considerations include the difficult selection of the best dosing to achieve efficacy while ensuring safety.

Recommendation 7.3:

*Cefiderocol represents a promising antibiotic option for patients with carbapenem-resistant *Acinetobacter baumannii* (CRAB) infections. Further studies are needed to consolidate this recommendation*

and to evaluate the use of cefiderocol as monotherapy or in combination with other antibiotics.

Strength of recommendation: **STRONG** Certainty of evidence: **LOW**

Rationale: Cefiderocol was recently approved by the FDA for the treatment of CRAB infections. Data on the use of this cephalosporin are limited and the certainty of evidence is low (Table 8). Cefiderocol was associated with similar clinical efficacy of BAT in the phase 3 CREDIBLE-CR study, which enrolled a heterogeneous population of patients with infections caused by CR-GNB [67]. In the subgroup of 54 patients (46% of all included subjects) who had CRAB infections, the all-cause mortality rate was higher in the cefiderocol group than in the BAT group (49% vs. 18%), but several confounding factors, such as renal dysfunction, ICU admission and septic shock, occurred more frequently in the cefiderocol group than in controls (septic shock 26% vs. 6%, respectively) [67]. A recent observational study including critically ill patients who received cefiderocol showed clinical success and 30-day mortality rates of 70% and 10%, respectively [99]. These findings are remarkable considering the severity of included patients and the high rates of clinical failure and mortality reported in studies investigating old antibiotics in this population. However, microbiological failure was reported in several patients and an increase in the MIC after cefiderocol therapy occurred in one patient [99]. The study has several limitations, including the small sample size and lack of a control group, but highlighted the promising role of cefiderocol in the treatment of CRAB infections [99].

Several aspects regarding the use of cefiderocol in patients with CRAB infections remain unresolved: PK/PD characteristics in patients with renal impairment and in critically ill patients; use of cefiderocol as monotherapy or in combination with other drugs; and penetration into the ELF and pulmonary concentrations in patients with VAP. Thus, consultation with an infectious diseases specialist should be recommended before its use.

The GRADE for this document was performed before the publication of new evidence about the treatment of CRAB infection. A recent observational study showed that cefiderocol, mainly used in combination with other antibiotics (tigecycline or fosfomycin in the majority of cases), is associated with reduced mortality rates compared with colistin-containing regimens in patients with BSI but not in those with VAP by CRAB. Since this is an observational study, it does not change the certainty of evidence of this recommendation (low), but adds an important piece of knowledge in the management of severe infections caused by CRAB [104]. In conclusion, despite low-quality of evidence, cefiderocol may be considered a promising therapeutic option for patients with CRAB infections. Further RCTs comparing cefiderocol-containing regimens vs. colistin-containing regimens are urgently warranted for an appropriate use of this new siderophore cephalosporin. GRADE for recommendations 6.1 (DTR-PA) and 7.1–7.3 (CRAB) are reported in Table 9.

Table 9
GRADE table for recommendations 6.1 (DTR-PA) and 7.1–7.3 (CRAB) (non-fermenting Gram-negative bacilli).

Recommendation	No. of studies	Study design	Risk of bias ^a	Inconsistency	Indirectness	Imprecision	Other considerations	Certainty of evidence
6.1	9 studies [67,82,83,68,86–90]	Three RCTs (for cefiderocol, imipenem/cilastatin–relebactam, and colistin alone vs. colistin plus meropenem) plus Three systematic reviews with meta-analysis (SR with MA) and three observational studies	No serious risk of bias for RCTs Serious risk of bias for observational studies and SR with MAs including mainly non-randomised studies	No serious inconsistency	No serious indirectness	Serious imprecision due to small sample sizes in many studies (often subset of larger studies investigating carbapenem-resistant infections)	No serious risk of publication bias	Moderate
6.2	9 studies [67,82,83,68,86–90]	Three RCTs (for cefiderocol, imipenem/cilastatin–relebactam, and colistin alone vs. colistin plus meropenem) plus Three systematic reviews with meta-analysis (SR with MA) and three observational studies	No serious risk of bias for RCTs Serious risk of bias for observational studies and SR with MAs including mainly non-randomised studies	Serious inconsistency (conflicting results from meta-analyses)	No serious indirectness	Serious imprecision due to small sample sizes in many studies (often subset of larger studies investigating carbapenem-resistant infections)	No serious risk of publication bias	Low
7.1–7.3	11 studies [67,88,91–99]	6 RCTs* 3 observational studies 2 systematic review with meta-analysis	Serious risk of bias for some of the RCTs	No serious inconsistency	No serious indirectness	Imprecision due to small sample sizes in many studies (both in observational studies and RCTs)	No serious risk of publication bias	Moderate/low

DTR-PA, *Pseudomonas aeruginosa* with difficult-to-treat resistance; CRAB, carbapenem-resistant *Acinetobacter baumannii*; RCT, randomised controlled trial. * 2/6 RCTs not registered on ClinicalTrial.gov.

^a For observational studies, risk of bias was assessed through the Newcastle–Ottawa Scale (NOS) [17], whereas for RCTs risk of bias was appraised through the Effective Practice and Organisation of Care guidelines [16]. High risk of bias converted to ‘very serious risk of bias’, low risk of bias converted to ‘no serious risk of bias’, whereas moderate/unclear risk of bias converted to ‘serious risk of bias’ or ‘no serious risk of bias’ according to evaluator judgement. For systematic reviews and meta-analyses, the quality assessment tool of the National Institutes of Health (NIH) was used [15].

QUESTION #8: What is the recommended treatment for methicillin-resistant *Staphylococcus aureus* (MRSA) infections?

Discussion of literature search strategy: Several drugs authorised by the European Medicines Agency (EMA) and/or the Italian Medicines Agency (AIFA) show *in vitro* activity against MRSA and are available for the treatment of infections caused by this organism in Italy. To develop evidence-based recommendations for the treatment of MRSA infections, we conducted a two-step systematic literature review. First, we searched for large RCTs published in the last 20 years that had assessed the efficacy for any indication of any drug with confirmed or potential anti-MRSA activity versus any other drug with confirmed or potential anti-MRSA activity (or versus no therapy/placebo for mild infections), provided that the compared drugs had been authorised by the EMA and/or AIFA for at least one indication, and independent of the number of MRSA infections enrolled. This initial step was necessary since many large RCTs of anti-MRSA agents were conducted per indication and not per pathogen. Consequently, if large enough (we set an arbitrary cut-off for inclusion of 200 patients), they could provide more precise evidence of efficacy for a given indication (narrower confidence interval if compared with a smaller RCT conducted only in patients with MRSA infection). We acknowledge that this strategy provides indirect evidence, but extrapolation to MRSA infections remains reasonable and justified by the large sample sizes of the included RCTs and the known *in vitro* anti-MRSA activity of the evaluated drugs. This first step allowed inclusion of as many as 31 RCTs assessing the efficacy of approved anti-MRSA drugs for the treatment of skin and soft-tissue infections (SSTIs) and as many as 8 RCTs assessing their efficacy for the treatment of pneumonia, which eventually allowed the development of recommendations for these two indications based on moderate to high certainty of evidence [105–143]. For the second step, starting again from title and abstract screening of the initial literature search results, we searched for RCTs for indications other than skin infections and pneumonia, this time with the restrictive inclusion criterion of at least 50 patients with proven MRSA infection. This allowed inclusion of five additional RCTs on MRSA bacteraemia [144–148]. The complete search strategy and the flow chart of study selection are available in the Supplementary material.

Skin and soft-tissue infections (SSTIs)

Recommendation 8.1:

Ceftaroline, dalbavancin, daptomycin, delafloxacin, linezolid, oritavancin and tedizolid are all possible alternatives to glycopeptides for the treatment of skin and soft-tissue infections (SSTIs) caused by methicillin-resistant Staphylococcus aureus (MRSA); the choice should not be exclusively based on costs and should be tailored to the individual patient according to the characteristics of the available drugs (availability of oral formulation, adherence to outpatient treatment, possibility of outpatient treatment or early discharge, toxicity profile)**.*

Strength of recommendation: **STRONG** Certainty of evidence: **HIGH**

* The lack of recent efficacy data from large RCTs for teicoplanin should be considered when making treatment choices, with other agents remaining preferential if not contraindicated.

** Source control should also be obtained whenever indicated. Favourable efficacy results for the treatment of acute bacterial skin and skin-structure infections (ABSSSIs) from a recent phase 3 RCT are also available for ceftobiprole, which could be considered as an additional alternative, provided it is authorised for this indication by AIFA. In selected cases when other agents are not indicated, telavancin could be considered as an alternative for the treatment of MRSA SSTIs, although a possible increased risk of nephrotoxicity should be considered. Tigecycline may be considered for non-severe SSTIs. Finally,

omadacycline also showed favourable efficacy results in phase 3 RCTs, but the application for EMA approval was withdrawn.

Rationale: Most of the large RCTs included in the systematic review were non-inferiority studies comparing agents with anti-MRSA activity vs. vancomycin for the treatment of SSTI or ABSSSIs [105–135]. While recognising that (i) changes occurred over the years in the definition of skin infections (e.g. from SSTI to ABSSSI) and that (ii) most large RCTs were not specifically designed to assess efficacy against MRSA skin infections, the certainty of evidence was eventually considered solid. This is because of the randomised design, the large populations, the known *in vitro* anti-MRSA activity of investigated agents, and the lack of substantial differences in clinical/microbiological cure rates between compared agents in subgroups of patients with MRSA skin infection across all studies (see Supplementary materials for detailed results).

Since achievement of non-inferiority was the rule in included studies, the panel deemed it appropriate to suggest factors other than efficacy to better guide the selection of antibacterials for MRSA infections on a case-by-case basis. These choices should not be based exclusively on costs, but should combine patient characteristics (organ insufficiency, allergy to certain antibiotic classes/drugs, need for hospitalisation, possibility of early discharge and/or outpatient treatment, adherence to outpatient treatment) and drug characteristics (toxicity profile, availability of oral formulation, long-acting activity, risk of *Clostridioides difficile* infection and costs) in order to select the most suitable agent for the needs of the individual patient, in line with principles of precision medicine.

Recommendation 8.2:

Trimethoprim/sulfamethoxazole (TMP/SMX) or clindamycin could be considered for outpatient treatment of mild, uncomplicated skin infections (after drainage of skin abscesses, if necessary).

Strength of recommendation: **CONDITIONAL** Certainty of evidence: **MODERATE**

Rationale: Five RCTs were included in our systematic review addressing the use of TMP/SMX and clindamycin for the outpatient treatment of uncomplicated skin abscesses or uncomplicated skin infections [116,128–130,132]. The frequency of patients with MRSA infection in the five studies ranged from 32% to 53%. In three studies [116,130,132], TMP/SMX and clindamycin were compared, showing comparable cure rates (see Supplementary Tables S27 and S28). In one of these three studies and in the other two remaining RCTs [116,128,129], treatment with TMP/SMX (or clindamycin in one study) was compared with placebo in all arms after abscess drainage. Although the direction of the effect was towards improved efficacy in all three studies, the large confidence intervals do not allow conclusions on superior efficacy over placebo in one of them. For this reason, while overall supporting the use of TMP/SMX or clindamycin for the outpatient treatment of uncomplicated MRSA skin infections, provided that the MRSA isolate is susceptible and in addition to drainage in case of skin abscesses, the certainty of evidence was deemed moderate. Finally, a RCT compared retapamulin ointment 1% vs. linezolid for the treatment of secondarily infected traumatic lesions and impetigo due to MRSA, showing lower cure rates in the retapamulin arm and thus not supporting its use [131].

Pneumonia

Recommendation 8.3:

Ceftobiprole, ceftaroline, linezolid or vancomycin are recommended for the treatment of community-acquired pneumonia (CAP) caused by methicillin-resistant Staphylococcus aureus (MRSA); the choice should not be exclusively based on costs and should be tailored to the individual patient according to the drug toxicity profile and susceptibility test results.

GOOD PRACTICE STATEMENT *	Based on the panel opinion (the available evidence was not deemed sufficient for developing a recommendation with GRADE methods)
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* Very few proven MRSA infections are registered in large RCTs in patients with CAP, therefore sufficient evidence for providing GRADE-based recommendation could not be extrapolated. The panel considered it appropriate to support the use of drugs with anti-MRSA activity approved for the treatment of CAP, including also lefamulin or delafloxacin when other agents are contraindicated.

Rationale: In line with the inclusion criteria of our systematic review, most large RCTs on CAP did not include patients with MRSA infection, except for two RCTs [141,142] that none the less included very few patients with MRSA infection (Supplementary materials). Consequently, sufficient evidence for providing GRADE-based recommendation could not be extrapolated. The panel considered it appropriate to support the use of drugs with anti-MRSA activity approved for the treatment of CAP, including also lefamulin or delafloxacin when other agents are contraindicated.

Recommendation 8.4:

Linezolid, ceftobiprole or vancomycin are recommended for the treatment of hospital-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) pneumonia in non-ventilated patients; the choice should not be exclusively based on costs and should be tailored to the individual patient according to the drug toxicity profile and susceptibility test results.

Strength of recommendation: **STRONG** Certainty of evidence: **HIGH**

Recommendation 8.5:

Linezolid or vancomycin are recommended for the treatment of ventilator-associated pneumonia (VAP) caused by methicillin-resistant *Staphylococcus aureus* (MRSA); the choice should not be exclusively based on costs and should be tailored to the individual patient according to the drug toxicity profile and susceptibility test results.

Strength of recommendation: **STRONG** Certainty of evidence: **HIGH**

Rationale: Our systematic review identified six large, double-blind RCTs, overall assessing the efficacy of linezolid, vancomycin, telavancin, tedizolid and ceftobiprole for the treatment of hospital-acquired pneumonia (HAP) and VAP [136–140,143]. Linezolid was compared with vancomycin in three RCTs [136–138] in which the frequency of patients with proven MRSA infection ranged from 32% to 100%. In the two RCTs not enrolling exclusively MRSA infections [137,138], similar clinical and microbiological cure rates were observed in the linezolid and vancomycin arms, whereas superior cure rates in the linezolid arm were observed in the study that enrolled only patients with respiratory or sputum specimens positive for MRSA [136]. Regarding tedizolid, its comparison with linezolid in a RCT conducted in patients with HAP or VAP likely caused by Gram-positive organisms resulted in similar 28-day mortality, but non-inferiority of tedizolid was not demonstrated for investigator-assessed clinical response [143]. In another RCT, telavancin was non-inferior to vancomycin for the treatment of HAP and VAP, although concerns were raised regarding a possibly increased risk of nephrotoxicity, leading the panel to support its use only when other recommended alternatives are unavailable/contraindicated [140]. Finally, ceftobiprole was non-inferior to ceftazidime plus linezolid for the treatment of HAP, although the results were not confirmed in the subgroup of patients with VAP, in which lower cure rates were observed in the ceftobiprole arm [139]. Overall, these results led the panel to recommend vancomycin and linezolid as possible first-line agents for the treatment of HAP and VAP involving MRSA (considering the increased efficacy of linezolid over vancomycin in one of three included RCTs comparing vancomycin versus linezolid), and ceftobiprole as a rea-

sonable alternative for HAP. For SSTIs, the panel reiterates that the choices among recommended agents should not be based exclusively on costs, but should combine patient and drug characteristics to select the most suitable agent for the needs of the individual patient, according to the principles of precision medicine.

Bacteraemia

Recommendation 8.6:

Daptomycin or vancomycin are recommended for the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) bacteraemia; the choice should not be exclusively based on costs and should be tailored to the individual patient according to the drug toxicity profile and susceptibility test results.

Strength of recommendation: **STRONG** Certainty of evidence: **MODERATE**

Recommendation 8.7:

Other anti-MRSA agents could be considered for the treatment of bacteraemia when daptomycin or vancomycin are contraindicated.

GOOD PRACTICE STATEMENT	Based on the panel opinion (the available evidence was not deemed sufficient for developing a recommendation with GRADE methods)
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Recommendation 8.8:

Pending further evidence from randomised controlled trials (RCTs), addition of fosfomycin to daptomycin, or of anti-staphylococcal penicillins (or other β -lactams), to vancomycin or daptomycin for the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) bacteraemia are reasonable choices for salvage treatment. The panel suggests that in selected cases of complicated MRSA bacteraemia, combination therapy could be considered as first-line treatment, although the current evidence remains inconclusive*.

GOOD PRACTICE STATEMENT	Based on the panel opinion (the available evidence was not deemed sufficient for developing a recommendation with GRADE methods)
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* A possible increased toxicity risk of these combinations, to be confirmed in further RCTs, should also be considered.

Rationale: Recommendation 8.6 is based on the results of an open-label, multicentre RCT showing non-inferiority of daptomycin to comparators (vancomycin in the case of MRSA, anti-staphylococcal penicillins in the case of methicillin-susceptible strains) in 235 patients with *S. aureus* bacteraemia and right-sided endocarditis [146]. In patients with MRSA infections, treatment success was 44.4% (20/45) in the daptomycin arm versus 31.8% (14/44) in the comparator arm (95% CI for difference, -7.4% to 32.6%). Overall, these results led the panel to recommend these two agents (pending the results of RCTs involving other anti-MRSA agents) for the treatment of MRSA bacteraemia. As for SSTIs and pneumonia, the panel underlines that the choices between these two agents should not be based exclusively on costs, but should consider patient and drug characteristics in order to select the most suitable agent for the needs of any individual patient, according to the principles of precision medicine.

When daptomycin or vancomycin cannot be used (allergy, resistance), in the opinion of the panel other agents (e.g. ceftobiprole, ceftaroline) may be considered for the treatment of MRSA bacteraemia, although this is a good practice statement based on expert opinion that considers the current lack of large RCTs and is motivated by the lack of approved alternatives in similar cases.

Regarding the addition of another agent (a β -lactam or fosfomycin) to vancomycin and daptomycin for the treatment of complicated MRSA bacteraemia (recommendation 8.8), which is a much-debated topic in the literature owing to the reported possibility of synergistic/additive effects in vitro, the panel do not exclude a possible benefit, although there are conflicting results stemming from currently available RCTs. Indeed, a RCT comparing

vancomycin or daptomycin plus an anti-staphylococcal penicillin or ceftazolin versus vancomycin or daptomycin for the treatment of MRSA bacteraemia was terminated early due to safety concerns regarding an increased cumulative incidence of acute kidney injury in the combination arm (23% vs. 6%) [145]. Conversely, in a RCT comparing vancomycin plus flucloxacillin versus vancomycin monotherapy for the treatment of MRSA bacteraemia [147], the mean time to resolution of bacteraemia in the combination group was 65% that of the time required for resolution in the standard therapy group (ratio of means 0.65; 95% CI 0.41–1.02%) according to a negative binomial model in the intention-to-treat-population, with the effect being more marked in the per-protocol population (see Supplementary Table S28 for more details). Finally, in a recent RCT comparing daptomycin plus fosfomycin for the treatment of MRSA bacteraemia (including endocarditis), treatment success was 54.1% and 42.0% in the combination and monotherapy arms, respectively (relative risk = 1.29, 95% CI 0.93–1.80) [148]. Adverse events leading to treatment discontinuation were registered in 17.6% and 4.9% of patients in the combination and monotherapy arms, respectively. Studies exploring the role of ceftaroline or ceftobiprole as companion agents to vancomycin or daptomycin were either observational or RCTs with a small sample size and were thus not considered for the present guideline. The panel remains open to future revision should results from larger RCTs regarding these combinations become available. In conclusion, while not discouraging the possible use of combinations in selected cases of complicated MRSA, especially for salvage treatment, this recommendation remains based on expert opinion only and should not be considered universal. Furthermore, the panel recognises that further study is needed to precisely identify the patient categories/phenotypes that may benefit from combination regimens as first-line treatment of MRSA infection.

General recommendations

Recommendation 8.9:

Trimethoprim/sulfamethoxazole (TMP/SMX) monotherapy should not be used for severe methicillin-resistant Staphylococcus aureus (MRSA) infections.

Strength of recommendation: **STRONG** Certainty of evidence: **LOW**

Rationale: This recommendation is based on an open-label RCT comparing TMP/SMX vs. vancomycin for the treatment of severe MRSA infections [142] in which the primary endpoint was treatment failure and TMP/SMX did not achieve non-inferiority to vancomycin (see Section 3 of Supplementary Table S28). Of note, the largest numerical difference in the rates of treatment failure was observed for bacteraemia [56% (23/41) and 40% (20/50) in TMP/SMX and vancomycin arms, respectively; risk ratio = 1.4, 95% CI 0.9–2.2]. Considering the open-label nature and the indirectness (heterogeneous types of infections) and imprecision of results (small sample), the certainty of evidence was deemed low but none the less sufficient in the opinion of the panel not to recommend TMP/SMX for the treatment of severe MRSA infections.

The certainty of evidence from the included RCTs on available agents for the treatment of MRSA infections in acute-care hospitals is reported in Table 10. GRADE for recommendations 8 (MRSA infections) are reported in Table 11.

QUESTION #9: What is the role of therapeutic drug monitoring (TDM) in the antimicrobial therapy of multidrug-resistant organism (MDRO) infections?

Discussion of literature search strategy: To address the role of TDM in the antimicrobial therapy of MDRO infections, primarily interventional and observational studies comparing TDM-based versus non-TDM-based therapeutic strategies were considered. When this kind of comparison was not available, recommendations regarding the most important antibiotic classes/agents were formu-

lated by the panel as best practices with the help of a skilled clinical pharmacologist, based on the most recent literature.

Recommendation 9.1:

In patients receiving vancomycin for the treatment of invasive methicillin-resistant Staphylococcus aureus (MRSA) infections, therapeutic drug monitoring (TDM) should be used to monitor drug plasma levels and dosing be adjusted accordingly; the target for therapeutic effectiveness is an AUC/MIC₂₄ ratio of 400–600 (assuming a vancomycin MIC of 1 mg/L) to maximise clinical efficacy while minimising toxicity risk.*

Strength of recommendation: **STRONG** Certainty of evidence: **LOW**

*Therapeutic target was extrapolated in a recent intersociety consensus [149].

Rationale: Vancomycin is a very important antibiotic in the management of severe Gram-positive infections, especially with MRSA, and is a first-line agent according to authoritative guidelines in several clinical scenarios [150]. As is well known, inappropriate vancomycin dosing is associated with therapeutic failure, the development of bacterial resistance and toxicity (primarily affecting the kidneys) [151]. TDM is widely acknowledged as a crucial component of vancomycin therapy management: safe and effective use of vancomycin requires compliance with recommendations regarding loading dose, TDM and dosage reduction in certain situations (e.g. renal impairment and other pathophysiological conditions) [152].

An important stone in the pyramid of evidence is a meta-analysis published in 2013 including studies comparing clinical outcomes of vancomycin therapy for Gram-positive infections in TDM-guided versus non-TDM-guided groups. TDM significantly improved clinical efficacy and decreased nephrotoxicity according to data from six studies, including one small RCT, but no specific data in the setting of MDRO infections could be extracted [153]. Subsequent observational studies confirmed the usefulness of TDM to guide vancomycin therapy [154–156]. Specific guidance for MRSA infections is provided in a recent international intersociety consensus, whose primary recommendation is to avoid routine monitoring of vancomycin serum peak concentrations in favour of a ratio of the area under the concentration–time curve over 24 h to the minimum inhibitory concentration (AUC₂₄/MIC) of ≥ 400 as the paramount PK/PD predictor of drug activity, as long as the vancomycin MIC is ≤ 1 mg/L in patients with normal renal function [149].

Recommendation 9.2:

Regarding β -lactams, therapeutic drug monitoring (TDM) plays an important role in maximising clinical efficacy, while reducing the likelihood of resistance emergence or toxicity.

GOOD PRACTICE STATEMENT Based on the panel opinion (the available evidence was not deemed sufficient for developing a recommendation with GRADE methods)

Recommendation 9.3:

Regarding linezolid, therapeutic drug monitoring (TDM) should be routinely performed when used in critically ill patients in order to maintain trough concentrations between 2 mg/L and 7 mg/L and to minimise the risk of haematological toxicity. Furthermore, critically ill patients exhibiting augmented renal clearance, obesity or infections caused by multidrug-resistant Gram-positive pathogens with an MIC ≥ 2 mg/L may require higher-than-standard linezolid dosage.

GOOD PRACTICE STATEMENT Based on the panel opinion (the available evidence was not deemed sufficient for developing a recommendation with GRADE methods)

Recommendation 9.4:

Regarding teicoplanin, therapeutic drug monitoring (TDM) should be routinely performed in critically ill patients owing to the significant

Table 10

Certainty of evidence from the included randomised controlled trials (RCTs) on available agents for the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) infections in acute-care hospitals.

Site of MRSA infection/ recommendation (R#)	Certainty of evidence in the evaluated RCTs ^a				Overall certainty of evidence ^b
	Very low	Low	Moderate	High	
SSTI					
R8.1	-	-	[105–108,125,126]	[109–115,117–124,127,133–135]	High
R8.2	-	-	[128]	[116,129,130,132]	Moderate
Pneumonia					
R8.3	-	-	[141,142]	-	Best practice
R8.4 and R8.5	-	-	-	[136–140,143]	High
Bacteraemia					
R8.6	-	[144]	-	[146]	Moderate
R8.7	-	-	-	-	Best practice
R8.8	-	[147]	[145,148]	-	Best practice
General					
R8.9	-	[144]	-	-	Low

SSTI, skin and soft-tissue infection.

^a For SSTI and pneumonia, certainty was considered high also when stemming from large high-quality RCTs on agents with anti-MRSA infections in which proven MRSA infections were only a subgroup (see the discussion of literature search strategy in the main document).

^b The overall certainty of evidence reflects a fully contextualised approach. For this reason, it is not the sum of the certainty of evidence stemming from the single studies, which may be limited only to a part of the question/s addressed by the recommendation (see the rationales for the different recommendations in the main document).

pharmacokinetic alterations commonly found (e.g. hypoalbuminaemia, variations in renal function, increase in volume of distribution).

GOOD PRACTICE STATEMENT Based on the panel opinion (the available evidence was not deemed sufficient for developing a recommendation with GRADE methods)

Recommendation 9.5:

Regarding daptomycin, considering its highly variable and unpredictable pharmacokinetic behaviour, therapeutic drug monitoring (TDM) should be performed in critically ill patients to evaluate efficacy or the occurrence of toxicity.

GOOD PRACTICE STATEMENT Based on the panel opinion (the available evidence was not deemed sufficient for developing a recommendation with GRADE methods)

Recommendation 9.6:

Regarding aminoglycosides, therapeutic drug monitoring (TDM) should be performed in critically ill patients to maximise achievement of an optimal C_{max}/MIC target, while minimising the occurrence of toxicity by monitoring trough concentrations.

GOOD PRACTICE STATEMENT Based on the panel opinion (the available evidence was not deemed sufficient for developing a recommendation with GRADE methods)

Rationale (for recommendations 9.2–9.6): For agents other than vancomycin, there is a paucity of high-quality data from RCTs comparing outcomes of TDM-guided versus non-TDM-guided approaches. Two small RCTs investigated meropenem and piperacillin/tazobactam, but no data could be inferred regarding the MDRO setting, and no relevant clinical impact was detected [157,158]. Nevertheless, recent guidelines and expert opinions have emphasised the importance of TDM-guided antibiotic dosage in critically ill patients. An expert panel including members of the Infection Section of the European Society of Intensive Care Medicine (ESICM), the Pharmacokinetic/pharmacodynamic and Critically Ill Patient Study Groups of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID), the Infectious Diseases Group of the International Association of Therapeutic Drug Monitoring and Clinical Toxicology (IATDMCT) and the Infections in the ICU and Sepsis Working Group of the International Society of Antimicrobial Chemotherapy (ISAC) [159] recommended TDM-guided dosing of aminoglycosides, β -lactams, linezolid, teicoplanin and vancomycin, while they neither recommend nor discourage

TDM for daptomycin, TMP/SMX, colistin and fluoroquinolones. Additionally, the French Society of Pharmacology and Therapeutics (Société Française de Pharmacologie et Thérapeutique-SFPT) and the French Society of Anesthesia and Intensive Care Medicine (Société Française d'Anesthésie et Réanimation-SFAR) [160] provided a specific recommendation (optional recommendation, strong agreement) for performing β -lactam TDM in ICU patients with expected pharmacokinetic variability and/or in patients with clinical signs potentially related to β -lactam toxicity, as well as subjects requiring continuous renal replacement therapy.

Several studies may support the routine implementation of a TDM-guided approach to achieve optimal PK/PD of β -lactams. In a multicentric prospective study, Roberts et al. found that 16% of 248 critically ill patients did not achieve a time with free drug concentration above MIC ($fT_{>MIC}$) of 50%, and these patients were 32% less likely to have a positive clinical outcome (OR = 0.68; $P = 0.009$) [161]. Positive clinical outcome was associated with increasing 50% $fT_{>MIC}$ and 100% $fT_{>MIC}$ ratios (OR = 1.02 and 1.56, respectively; $P < 0.03$), with significant interaction with illness severity status. Furthermore, several other studies showed the importance of a TDM-guided approach in optimising β -lactam dosage to achieve the best PK/PD target, although a comparison with subjects without TDM was not performed [162–165].

Regarding linezolid, Pea et al. reported overexposure in 33% of patients, being severe (>20 mg/L) in 3.9% of cases, while underexposure was less frequent (16.2%), thus justifying the importance of monitoring linezolid plasma concentrations [166]. Similarly, Pea et al. suggest that TDM might be especially useful for avoiding dose-dependent toxicity or treatment failure in $\sim 30\%$ of cases, noting that the optimal PK/PD target [trough level (C_{min}) > 2 mg/L] was achieved in only 60–70% of patients treated with linezolid [167]. Cojutti et al. found a significantly higher incidence of thrombocytopenia in patients with persistent linezolid overexposure compared with subjects who had target linezolid serum levels or experienced transient linezolid overexposure [168]. Additionally, thrombocytopenia was independently associated with median linezolid C_{min} values.

Regarding teicoplanin, Pea et al. found that only 35% of 202 critically ill patients achieved adequate teicoplanin exposure after 4 days of treatment, thus justifying the importance of TDM to ensure that dose regimens are optimised to the individual requirements of the patient [169].

Table 11
GRADE table for recommendation 8 regarding methicillin-resistant *Staphylococcus aureus* (MRSA) infections.

Recommendation	No. of studies	Studies design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Certainty of evidence
8.1	25 studies [105–115,117–127,133–135]	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness (the evaluators judged it reasonable to extrapolate evidence from large RCTs per indication, see discussion of search strategy in the manuscript)	No serious imprecision	No other considerations	High
8.2	5 studies [116,128–130,132]	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness (the evaluators judged it reasonable to extrapolate evidence from large RCTs per indication, see discussion of search strategy in the manuscript)	No serious imprecision (although some included studies were possibly underpowered)	No other considerations	Moderate
8.4	6 studies [136–140,143]	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness (the evaluators judged it reasonable to extrapolate evidence from large RCTs per indication, see discussion of search strategy in the manuscript)	No serious imprecision	No other considerations	High
8.5	6 studies [136–140,143]	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness (the evaluators judged it reasonable to extrapolate evidence from large RCTs per indication, see discussion of search strategy in the manuscript)	No serious imprecision	No other considerations	High
8.6	2 studies [144,146]	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Direct comparison of daptomycin and vancomycin only in one study	Moderate
8.9	1 study [144]	RCT	No serious risk of bias	No serious inconsistency	Serious indirectness (heterogeneous types of infections)	Serious imprecision (it should be noted that the effect was apparently largest in the bacteraemia subgroup)	The included study was open-label	Low

RCT, randomised controlled trial.

Regarding daptomycin, Galar et al. found large interindividual variability in serum daptomycin levels collected in 63 different patients, reporting that trough concentrations < 3.2 mg/L were independently associated with poor outcomes (OR = 6.465, 95% CI 1.032–40.087; *P* = 0.046) [170]. Consequently, TDM could be a useful strategy to optimise daptomycin dosing and to avoid therapeutic failure. Furthermore, TDM may be a useful strategy also to avoid the occurrence of daptomycin toxicity. Bhavnani et al. demonstrated that creatine phosphokinase elevation was significantly associated with daptomycin *C*_{min} above 24.3 mg/L [171].

Regarding aminoglycosides, van Lent-Evers et al. found that an active TDM approach (implemented in 105 patients) led to significantly more achievement of optimal aminoglycoside peak and trough concentrations (*P* < 0.01) compared with 127 patients not using an adaptive TDM-guided strategy, resulting in significantly lower mortality rate in patients admitted with a proven infection (*P* = 0.023), reduced hospital LOS (*P* = 0.045) and a lower incidence of nephrotoxicity (*P* < 0.01) [172].

In conclusion, the use of TDM for many classes of antibiotics may be very useful, especially in the context of MDRO infections and/or critically ill patients. More high-quality studies, designed according to best available knowledge on TDM [173], are needed to better define its role for the most important antimicrobials. GRADE for recommendation 9.1 is reported in Table 12.

QUESTION #10: What is the role of follow-up blood cultures (FUBCs) in the management of multidrug-resistant organism bloodstream infection (MDRO-BSI)?

Discussion of literature search strategy: To address the question of the role of FUBCs in the management of Gram-negative or Gram-positive MDRO-BSIs, the literature search focused on interventional and observational studies investigating the clinical impact of FUBCs. Studies only reporting the FUBC results were excluded; studies were only included if they reported how performing FUBC could affect at least one clinical outcome (e.g. survival, duration of therapy).

Recommendation 10.1:

In patients affected by methicillin-resistant Staphylococcus aureus bloodstream infection (MRSA-BSI), performing follow-up blood cultures (FUBCs) to detect bacteraemia persistence in the context of a bundle of interventions (e.g. infectious diseases consultation, early source control, echocardiography) may positively impact on relevant clinical outcomes; the exact timing of follow-up still needs to be established.

Strength of recommendation: **STRONG** Certainty of evidence: **LOW**

Rationale: *Staphylococcus aureus* BSI is a serious infection, often characterised by a complicated course with metastatic infections (e.g. endocarditis, vertebral osteomyelitis, involvement of prosthetic material) [174]. It represents one of the leading causes both of community-acquired and healthcare-associated bacteraemia, showing a mortality rate of at least 20–30% [174]. In particular, MRSA poses a huge clinical threat, with persistently high morbidity and mortality [175]. The management of MRSA-BSI requires a co-ordinated series of actions, a bundle including appropriate antimicrobial treatment and non-antibiotic therapeutic interventions that may include early source control when needed, echocardiography to diagnose or rule out endocarditis, and FUBC [174,176]. *Staphylococcus aureus* is by far the most common organism responsible for persistent bacteraemia independent of infection source, thereby FUBCs are appropriate when this pathogen is detected in blood culture in order to determine whether the infection is complicated/persistent and consequently the duration of therapy needed [177,178]. Moreover, optimal management of *S. aureus* BSI should aim to achieve microbiological clearance as soon as possible in order to reduce the incremental risk of mortality

Table 12
GRADE table for recommendation 9.1.

No. of studies	Study design	Risk of bias ^a	Inconsistency	Indirectness	Imprecision	Other considerations	Certainty of evidence
4 [153–156]	One meta-analysis (including only one RCT and five cohort studies), one quasi-experimental study and two observational studies	Serious risk of bias due to confounding	Serious inconsistency (not consistent direction of effect for all outcomes)	Serious indirectness (mixed population of MSSA and MRSA infections in many cases)	Serious imprecision due to small sample sizes in many studies	No serious risk of publication bias	Low (consistent direction of effect for clinical efficacy and toxicity, but conflicting evidence for mortality)

RCT, randomised controlled trial; MSSA, methicillin-susceptible *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*.

^a For observational studies, risk of bias was assessed through the Newcastle–Ottawa Scale (NOS) [17], whereas for RCTs risk of bias was appraised through the Effective Practice and Organisation of Care guidelines [16]. High risk of bias converted to 'very serious risk of bias', low risk of bias converted to 'no serious risk of bias', whereas moderate/unclear risk of bias converted to 'serious risk of bias' or 'no serious risk of bias' according to evaluator judgement. For systematic reviews and meta-analyses, the quality assessment tool of the National Institutes of Health (NIH) was used [15].

with each day of positive blood culture, as shown in a study of 884 infective episodes (13.4% by MRSA) in which metastatic complications, LOS and 30-day mortality were progressively worse as bacteraemia duration increased ($P < 0.0001$) [179]. Currently, no prospective controlled trial has randomly assigned patients with an index MRSA-positive blood culture to undergo FUBCs or not; however, observational evidence clearly points to the usefulness of FUBCs [180–188]. Conducting FUBCs is itself associated with lower mortality, explaining why they are considered a quality indicator in MRSA-BSI care [189]. Moreover, negative FUBCs are usually associated with improved overall survival. Limitations of these studies arise from their observational nature and the fact that many cohorts included both MRSA and their methicillin-susceptible counterparts, but although the antibiotic options are different, the principles and general approach to *S. aureus* BSI are the same irrespective of the resistance profile [178]. Another aspect to be elucidated is the best timing for FUBCs. According to current guidelines, they should be performed within 48–96 h after the initial set of positive blood cultures (not later than 4 days), possibly under appropriate antimicrobial treatment, which is generally started empirically when blood cultures are drawn [176,178]. A recent study on 987 BSIs involving *S. aureus* (11% MRSA), all with FUBCs that were positive up to 7 days from index cultures, suggested redefining the cut-off duration for persistent bacteraemia (currently recommended at 48–72 h) and instead performing the first FUBCs at 24 h, which was both the earliest and the most relevant differentiator of 90-day mortality [adjusted hazard ratio (HR) = 1.93, 95% CI 1.51–2.46] [187].

Recommendation 10.2:

In patients affected by vancomycin-resistant enterococci bloodstream infection (VRE-BSI), performing follow-up blood cultures (FUBCs) to detect bacteraemia persistence in the context of a bundle of interventions (e.g. infectious diseases consultation, early source control, echocardiography) may positively influence important clinical outcomes; the best timing of follow-up still needs to be established.

Strength of recommendation:	CONDITIONAL	Certainty of evidence:	VERY LOW
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Rationale: *Enterococcus* spp. are among the leading causative micro-organisms in BSIs, particularly in healthcare settings, usually affecting fragile patients such as the elderly and immunosuppressed [190]. Mortality rates are high ($\geq 20\%$), especially in cases of endocarditis, which represents a frequent complication [191]. The approach to *Enterococcus* spp. is further complicated by the fact that the bacteria often harbour multiple and complex mechanisms of resistance, primarily to vancomycin (i.e. VRE) leading to challenging clinical scenarios [192]. Notwithstanding the obvious differences between the two types of bacteria, the general management of *Enterococcus* spp. BSI overlaps that of *S. aureus* BSI: a bundle of actions including infectious diseases consultation, FUBCs, echocardiography and early targeted antibiotic treatment is associated with lower short- and long-term mortality [193,194]. Specifically, performing FUBCs was associated with improved survival (at univariate analysis) in a large cohort of enterococcal BSIs, although only 3 of 368 episodes were ascribable to VRE [194]. In a retrospective cohort investigating only VRE among 71 cases of enterococcal BSI, patients with positive FUBCs showed a 4-fold increased risk of mortality, demonstrating the useful prognostic role of repeat cultures in this setting [195]. As with MRSA-BSI, the best timing to perform FUBCs in VRE-BSI needs to be established.

Recommendation 10.3:

In patients affected by Gram-negative bloodstream infection (BSI), performing follow-up blood cultures (FUBCs) may have a useful prognostic role, especially in case of severe and/or high-inoculum infections, non-eradicable foci or immunosuppressed patients.

Strength of recommendation:	CONDITIONAL	Certainty of evidence:	VERY LOW
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Rationale: If FUBCs, on the one hand, have become a relevant component of the management of the paradigmatic Gram-positive BSIs (by *S. aureus* and *Enterococcus*, which share a high propensity for endovascular and metastatic infections), their role in Gram-negative BSI is more debated. Repeat cultures are usually not indicated in case of uncomplicated bacteraemia: generally, this concept implies the absence of a persistent or difficult-to-eradicate infectious source [196]. The optimal management of Gram-negative BSI in hospitalised patients is rapidly evolving due to the recognition of drivers of persistent bacteraemia: involvement of a MDRO as causative agent, severe infections (e.g. septic shock) and immunosuppression [197]. Focusing on MDR Gram-negative BSIs, screening of the literature aimed at investigating the clinical impact of FUBCs in this setting revealed serious inconsistency, indirectness and imprecision [182,195,198–206]. Indeed, populations were quite heterogeneous and the percentage of FUBCs performed and the yield of repeat cultures varied widely; moreover, only one study specifically addressed solely CR-GNB [195]. In this study, negative results of FUBCs, defined as more than one separate blood culture taken >24 h after the initial blood culture, emerged as an independent predictor of 28-day survival (adjusted OR for mortality 0.25, 95% CI 0.09–0.62) [195]. Data from the largest observational studies on the topic seem to confirm the usefulness of FUBCs: in a prospective US cohort of 1702 patients with Gram-negative BSI (39% with neoplasms in medical history), FUBCs were performed 24 h to 7 days after the index culture in 1164 cases, and 20% were positive for persistent infection [204]. A propensity score-weighted model showed that FUBCs were associated with lower rates of all-cause mortality (HR = 0.63, 95% CI 0.51–0.77); the mortality rate was significantly higher among patients with persistent infection detected at FUBC (49/228, 21%) than among patients with negative FUBCs (110/885; 11%; $P = 0.0005$) [204]. Coherently, in an Italian retrospective cohort of 1576 patients with Gram-negative BSI (mean Charlson score 6, 8.9% with carbapenem-resistant pathogens), performing FUBCs was associated with better survival (adjusted HR for mortality 0.48, 95% CI 0.27–0.83); in this cohort, FUBCs were obtained in 17.6% of patients (278/1576) within a median of 3 days after the index culture and 2 days after initiating active therapy; persistent BSI was found in 107 patients (38.5%) [202]. In some patients, persistence of bacteraemia at FUBC in the context of Gram-negative BSI may be a marker of septic thrombophlebitis, an infrequent but often lethal complication of endovascular infections [206]. These findings pave the way for RCTs aimed at directly assessing outcomes for Gram-negative BSI with or without routine FUBC [207]. Another type of study that could add strong evidence to the role of FUBCs in this setting should evaluate risk factors for positive FUBC and devise a score system to identify the need for FUBCs in patients with Gram-negative BSIs [203]. Pending further data, the panel considers performing FUBCs in patients with MDR Gram-negative BSI a reasonable strategy, especially in case of severe and/or high-inoculum infections, non-eradicable foci and immunosuppressed patients. GRADE for recommendations 10.1–10.3 is reported in Table 13.

Expert opinion

The present document provides updated recommendations on the diagnosis and targeted treatment of infections due to priority resistant bacteria (CRE, DTR-PA, CRAB and MRSA) in daily clinical practice. The recommendations consider three crucial recent innovations: (i) the availability of new β -lactams active against CR-GNB; (ii) the differential activity of novel antibacterials by type of resistance determinants; and (iii) the availability of novel tests

Table 13
GRADE table for recommendations 10.1–10.3.

Recommendation	No. of studies	Study design	Risk of bias ^a	Inconsistency	Indirectness	Imprecision	Other considerations	Certainty of evidence
10.1	9 [180–188]	Observational studies	Serious risk of bias due to confounding	No serious inconsistency	No serious indirectness	Serious imprecision due to small sample sizes in many studies	No serious risk of publication bias	Low (consistent direction of effect in adjusted analyses) Very low
10.2	2 [194,195]	Observational studies	Serious risk of bias due to confounding	No serious inconsistency	Serious indirectness due to mixed population in one study (VRE and non-VRE)	Serious imprecision due to the limited number of studies	No serious risk of publication bias	Very low
10.3	11 [182,195,198–206]	Observational studies	Serious risk of bias due to confounding	Serious inconsistency owing to different outcomes assessed	Serious indirectness due to mixed population (MDRO and non-MDRO)	Serious imprecision due to the limited sample size when considering only the subset of MDRO population	No serious risk of publication bias	Very low

VRE, vancomycin-resistant enterococci; MDRO, multidrug-resistant organism.

^a For observational studies, risk of bias was assessed through the Newcastle–Ottawa Scale (NOS) [17]. High risk of bias converted to ‘very serious risk of bias’, low risk of bias converted to ‘no serious risk of bias’, whereas moderate/unclear risk of bias converted to ‘serious risk of bias’ or ‘no serious risk of bias’ according to evaluator judgement.

for the rapid identification of bacteria and/or resistance determinants. The introduction of these innovations in clinical practice is progressively changing our approach to the treatment of resistant infections, since novel considerations (e.g. rapid aetiological diagnosis and antibiogram, choice of early targeted treatment based on resistance determinants) are now included in the clinical reasoning at the bedside of infected patients.

In this new scenario, evidence-based recommendations are crucial for the use both of old and novel antibacterial agents for the treatment of infections due to priority resistant bacteria. The use of novel agents should be guided by two important considerations: (i) the need to preserve their activity through rational use according to antimicrobial stewardship principles; and (ii) the parallel need to use them without hesitation when they are the most effective options, or the safest options among equally effective options. Importantly, these two considerations are not mutually exclusive. Indeed, the right balance is needed between excessively parsimonious use (risk of using less efficacious and/or more toxic alternative options) and indiscriminate use (risk of unnecessary selection of resistance without additional benefits to patients). Against this backdrop, the use of RDTs may be pivotal in allowing early targeted treatment, whereas the appropriate use of TDM may reduce the risk both of resistance selection and toxicity by providing precious indications for optimising antibacterial dosages during treatment.

These recommendations provide a rigorous, systematic update of the available evidence to guide treatment of resistant infections through a global approach that considers laboratory diagnosis, use of TDM and the role of FUBCs. They are updated to the time of its release, and future revisions will be provided as evidence from high-quality studies accrues. In general, two main trends stem from the current literature and the recommendations provided: (i) for infections caused by resistant Gram-negative bacteria, clinical reasoning is moving towards rapid identification of the causative agents and, especially for CPE, of their resistance determinants, in order to guide early targeted treatment; and (ii) for the treatment of MRSA infections, the availability of several active agents with similar expected efficacies allows treatment to be adapted to the individual patient (e.g. avoidance of hospitalisation, early discharge, poor adherence to treatment) and to the site of infection and label indications (e.g. ABSSSI, pneumonia, BSI). A third consideration, connected to the previous two, is that high-certainty evidence remains scarce for the treatment of CRAB infections and, in general, for infections other than pneumonia, ABSSSI, complicated intra-abdominal infection (for anti-Gram-negative agents) and BSI. In this regard, the recent increase in the number of pathogen-oriented rather than indication-oriented RCTs may help to smooth these important limitations in the future.

Recommendations on duration of therapy are not provided, but clinicians are advised that the duration of therapy should not differ for infections caused by organisms with resistant phenotypes compared with infections caused by more susceptible phenotypes, but may depend on other factors. The optimal timing of administration of *in vitro*-active antibiotics may have a role in reducing the duration of antibiotic therapy. Thus, the panel agree that the early start of an empirical therapy tailored on rectal colonisation status, risk factors and disease severity of the patient, together with a prompt de-escalation as soon as susceptibility tests are available, is a recommended strategy and may increase the clinical response while reducing the need of prolonged antibiotic therapy. Additionally, important host factors related to immune status, ability to attain source control, and response to therapy should be considered when determining treatment durations for antimicrobial-resistant infections. Finally, whenever possible, oral step-down therapy should be considered, if the following criteria are met: (i) susceptibility to an appropriate oral agent is demon-

strated; (ii) the patient is haemodynamically stable; (iii) reasonable source control measures have taken place; (iv) the patient is able to maintain oral intake; and (v) concerns about insufficient intestinal absorption are not present.

This document also has some limitations. First, we formulated some discordant recommendations (defined as strong recommendations based on low-quality evidence). This approach is debated and some recent opinion articles suggest to avoid it [208,209]. However, not all discordant recommendations are equally problematic and discouraged. The WHO provided guidance to identify some situations in which strong recommendations may be indicated despite low or very low confidence in effect estimates [210]. According to the WHO guidance, we provided discordant recommendations in the following situations: (i) life-threatening situations (e.g. recommendations 1.3, 8.9 and 10.1); and (ii) situations in which one therapeutic option may be potentially more risky than the other (e.g. recommendations 7.3 and 9.1). Second, we provided many good practice recommendations based on the fact that the available evidence was not deemed sufficient for developing a recommendation with GRADE methods. We decided to provide a 'Good practice statement', instead of 'No recommendation can be made' owing to the pragmatic nature of this document. Moreover, in these cases the panel agree that, despite the low available literature, some statements may significantly help clinicians to manage patients with difficult-to-treat infections. Anyway, the guideline panel addressed the required issues before making good practice statements [211,212]. Third, since studies evaluating the clinical utility of RDTs are heterogeneous, we did not discriminate type of recommendations according to different types of RDTs (RDTs able to identify pathogens vs. molecular RDTs able to identify resistance genes). In general, we suggest that each facility should implement the use of molecular RDTs. Further documents should examine differences in the efficacy of different types of RDT in improving patient outcomes. Moreover, value of RDTs in infections other than BSIs (such as low respiratory tract infections) is less studied. In these cases, the differentiation between pathogens and colonisers is extremely difficult and the misuse of RDTs free from a clinical interpretation of the data may lead to antibiotic overuse. Thus, we suggest awareness about the interpretation of RDT results according to the clinical status of the patient. Detection of specific resistance genes does not cover all resistance mechanisms (e.g. genes encoding efflux pumps are seldom detected). The co-existence (co-detection) of these mechanisms (enzymatic mechanisms such as β -lactamases and loss of membrane porin) does not provide information regarding susceptible antibiotics and should be further explored. Finally, this document did not address the duration of antibacterial therapy and antimicrobial dosages, two topics that none the less also incorporates non-MDRO infections and could thus merit a separated, dedicated assessment in the forthcoming future.

Conclusions

Although important work remains in terms of establishing a global approach to treating infections due to priority resistant bacteria, the present document provides physicians with updated, evidence-based recommendations to guide the proper treatment of resistant infections in line with the principles of precision medicine.

Acknowledgment

The authors thank Andrea Cifani (Ethos S.r.l.) for organisation of experts meeting and writing assistance.

Funding

This work was supported by Italian Society of Infection and Tropical Diseases (SIMIT), the Italian Society of Anti-Infective Therapy (SITA), the Italian Group for Antimicrobial Stewardship (GISA), the Italian Association of Clinical Microbiologists (AMCLI) and the Italian Society of Microbiology (SIM).

Competing interests

DRG reports advisory board and/or speaker honoraria from Pfizer and Tillotts Pharma, and investigator-initiated grants from Gilead, Pfizer and Shionogi; MF has received grants and/or speaker honoraria from MSD, Angelini, Shionogi, Pfizer, Menarini, Gilead, TermoFisher, and Nordic Pharma; MG has received honoraria for lectures, presentations or speakers bureaus from MSD, Shionogi, Pfizer and Gilead and for participation on a data safety monitoring board or advisory board from MSD and Pfizer; FP reports personal fees from Angelini, Basilea Pharmaceutica, Gilead, Hikma, MSD, Pfizer, Sanofi Aventis, Shionogi, Thermo Fisher and Accelerate Diagnostics, and has participated in speaker's bureau for Accelerate Diagnostics, Angelini, Basilea Pharmaceutica, Gilead, Hikma, MSD, Pfizer, Sanofi Aventis, Shionogi, Thermo Fisher and as consultant for Angelini, Basilea Pharmaceutica, Gilead, MSD, Pfizer and Shionogi; GMR has participated in advisory boards and speaker's bureau for, and received research contracts, contributions and travel grants from Accelerate, Angelini, Arrow, Beckman Biomedical Service, Coulter, Becton Dickinson, bioMérieux, Cepheid, Hain Life Sciences, Menarini, Meridian, MSD, Nordic Pharma, Pfizer, Qiagen, Q-linea, Qpex, Quidel, Qvella, Roche, Seegene, Set-Lance, Shionogi, Symcel, Thermo Fisher, VenatorX and Zambon; MV reports honoraria for lectures, presentations or speakers bureaus from Pfizer, Correvio, Shionogi, Angelini and Menarini; MB has received research grants and/or advisor/consultant and/or speaker/chairman fees from Bayer, bioMérieux, Cidara, Cipla, Gilead, Menarini, MSD, Pfizer and Shionogi; FM has participated in advisory boards and/or received speaker honoraria from Angelini, Correvio, Merck Sharp & Dohme (MSD), Nordic Pharma, Pfizer, Astellas, Gilead, Bristol-Myers Squibb (BMS), Janssen, ViiV, bioMérieux, Biotest, Becton Dickinson, Pfizer and Shionogi; MT reports consulting fees from Fresenius-Kabi and Effetti, honoraria for speakers bureaus or educational events from Fondazione Iniziative Zooprofilattiche e Zootecniche-Brescia and Progetto Meeting – Bologna, and support for attending meetings and/or travel from SIMIT. All other authors declare no competing interests.

Ethical approval

Not required.

Sequence information

Not applicable.
TS: add in link

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.ijantimicag.2022.106611](https://doi.org/10.1016/j.ijantimicag.2022.106611).

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