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Review

Management of infections caused by WHO critical priority Gram-negative pathogens in Arab countries of the Middle East: a consensus paper

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A B S T R A C T

Antimicrobial resistance is an important global issue that impacts the efficacy of established antimicrobial therapy. This is true globally and within the Arab countries of the Middle East, where a range of key Gram-negative pathogens pose challenges to effective therapy. There is a need to establish effective treatment recommendations for this region given specific challenges to antimicrobial therapy, including variations in the availability of antimicrobials, infrastructure and specialist expertise. This consensus provides regional recommendations for the first-line treatment of hospitalized patients with serious infections caused by World Health Organization critical priority Gram-negative pathogens *Acinetobacter baumannii* and *Pseudomonas aeruginosa* resistant to carbapenems, and Enterobacteriaceae resistant to carbapenems and third-generation cephalosporins. A working group comprising experts in infectious disease across the region was assembled to review contemporary literature and provide additional consensus on the treatment of key pathogens. Detailed therapeutic recommendations are formulated for these pathogens with a focus on bacteraemia, nosocomial pneumonia, urinary tract infections, skin and soft tissue infections, and intra-abdominal infections. First-line treatment options are provided, along with alternative agents that may be used where variations in antimicrobial availability exist or where local preferences and resistance patterns should be considered. These recommendations take into consideration the diverse social and healthcare structures of the Arab countries of the Middle East, meeting a need that is not filled by international guidelines. There is a need for these recommendations to be updated continually to reflect changes in antimicrobial resistance in the region, as well as drug availability and emerging data from clinical trials.

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1. Introduction

The prevalence of multi-drug-resistant (MDR) pathogens has been increasing worldwide, including in the Arab countries of the Middle East [1]. Judicious use of antibiotics is crucial for the prevention of further emergence and spread of antimicrobial resistance (AMR) [1]. Appropriate use of antimicrobial therapy is mainly dependent on the availability of regional epidemiological data and resistance profiles [1].

Epidemiological resistance patterns in Arab countries of the Middle East are not homogeneous (Fig. 1) [1–6]. A recent review of the epidemiology of common resistant bacterial pathogens in Arab countries found vast variations across the region [1]. Rates of extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae ranged from 4% to 31%; *CTX-M* was the most commonly reported resistant gene [1,7]. The prevalence of carbapenem-resistant Enterobacteriaceae (CRE) *Escherichia coli* and *Klebsiella* spp. ranged from 1% to 7% [1]. More recently, tertiary care centres across the region have observed an increase in the rate of CRE [8,9]. The most commonly produced carbapenemases were NDM-1 (46.5%), OXA-48 (32.5%) or both (8.9%) [1,10]. In some hospitals in Bahrain and Saudi Arabia, OXA-48 was more prevalent than NDM-1 [11]. *Klebsiella pneumoniae* carbapenemase (KPC) enzymes have been detected in small numbers in Saudi Arabia [12], and colistin-resistant *E. coli* isolates carrying the *mcr1* gene have also been reported [13]. The prevalence of carbapenem-resistant *Pseudomonas aeruginosa* ranged from 3% to 28% [1]. The production of metallo-β-lactamases (mainly VIM and IMP) is cited as the most important mechanism of resistance [1,14], but rare enzymes, such as PME-1 in Qatar, have also been reported [15]. *Acinetobacter* spp. remain one of the most common pathogens encountered in hospital-acquired infections in some Arab countries of the Middle East; they are mainly MDR and particularly carbapenem resistant [16,17]. The prevalence of carbapenem-resistant *Acinetobacter baumannii* (CRAB) ranged from 36% to 100% [1,16], and colistin resistance has also been reported [18]. Most CRAB isolates harboured the *blaOXA-51* and *blaOXA-23* genes [19,20], with rapid emergence of NDM-1 [1,14].

There is also variation between Arab countries of the Middle East in terms of the availability of antimicrobials, diagnostic technologies, laboratory supplies and trained specialized personnel. Regional guidelines for the management of MDR infections that can be tailored to the local sociodemographic and economic particularities in Arab countries of the Middle East have been highlighted as a necessity for the region [1].

This consensus provides regionally based recommendations for the first-line treatment of hospitalized patients with serious infections caused by the World Health Organization (WHO) critical priority Gram-negative pathogens *A. baumannii* and *P. aeruginosa* resistant to carbapenems, and Enterobacteriaceae resistant to carbapenems and third-generation cephalosporins.

2. Methods

A mixed working group comprising experts in microbiology, infectious disease and intensive care medicine from Arab countries of the Middle East first convened in November 2018. The working group members were chosen based on their expertise in the management of MDR infections, with each expert representing their

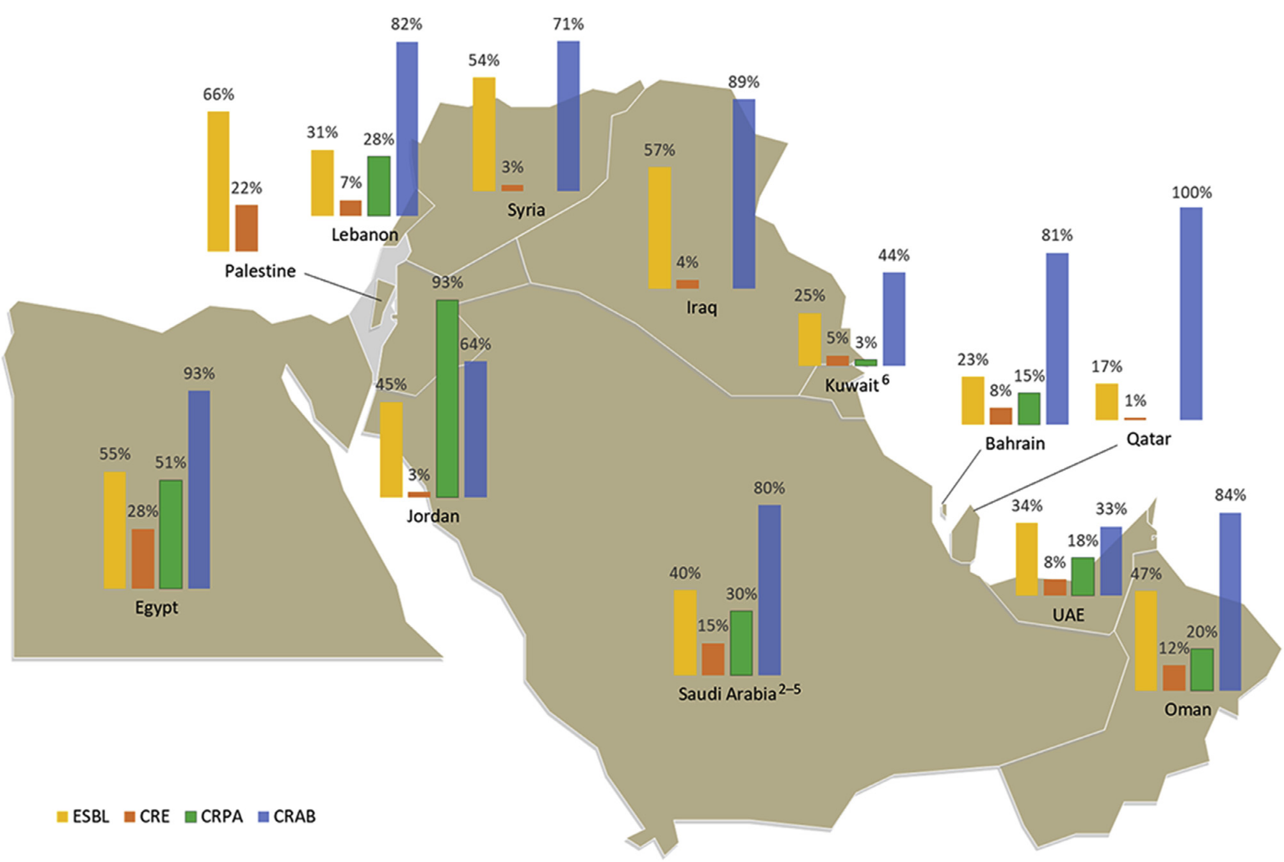

Fig. 1. Prevalence (%) of multi-drug-resistant Gram-negative pathogens in the Arab countries of the Middle East [1–6]. Where available, the most recent Global Antimicrobial Resistance Surveillance System data are used for these figures; other data are extracted from published literature reported by hospitals in the respective country and do not represent national data (data currently unpublished, personal communication from authors). Where a range of data exist for a country, the upper end of range is displayed on the graph [Bahrain: CRE 1–8% and CRAB 80–81%; UAE: ESBL 28.6–34.2%]. CRAB, carbapenem-resistant *Acinetobacter baumannii*; CRE, carbapenem-resistant Enterobacteriaceae; CRPA, carbapenem-resistant *Pseudomonas aeruginosa*; ESBL, extended-spectrum beta-lactamase; UAE, United Arab Emirates.

country as either a leading infectious disease researcher, an eminent clinical microbiologist or an antimicrobial stewardship lead. The working group agreed unanimously on the need for a regional perspective on the implementation of international guidelines for the treatment of MDR infections, and identified *A. baumannii*, Enterobacteriaceae and *P. aeruginosa* as the top pathogens of concern. The scope for treatment recommendations was limited to serious infections in hospitalized patients. This was further refined to focus on the most common infection types in the region, which were identified by the working group as bacteraemia, nosocomial pneumonia, urinary tract infections (UTIs) and complicated skin and soft tissue infections (cSSTIs). As Enterobacteriaceae are the most frequently isolated pathogens in complicated intra-abdominal infections (cIAIs) [21,22], recommendations for the treatment of ESBL-producing Enterobacteriaceae (cIAI) were also included.

A literature search was conducted in PubMed using pertinent keywords (e.g. 'multidrug resistant', 'Gram-negative bacterial infections', '*Pseudomonas*', '*Acinetobacter*', '*Klebsiella*', 'Enterobacteriaceae') to identify international, regional and local guidelines dating back 5 years from 2014 to 2019 for the treatment of infections caused by *A. baumannii*, Enterobacteriaceae and *P. aeruginosa*. A second literature search was undertaken in PubMed using the same pertinent keywords as in the previous search complemented by regional identifiers (e.g. 'Middle East', 'Levant', 'Gulf', 'Arab') to identify articles related to the treatment of *A. baumannii*, Enterobacteriaceae and *P. aeruginosa* in Arab countries of the Middle East dating back 10 years from 2009 to 2019. This longer timespan was endorsed to ensure that all relevant publications were captured given the lack of regionally specific literature. Articles extracted in full also underwent manual review of their bibliographies in order to identify additional potentially relevant publications. This literature search provided the basis for the working group in developing their consensus recommendations.

The working group split into subgroups and each subgroup was assigned a pathogen on which to develop treatment recommendations, based on review of the literature and expert clinical opinion (in the absence of scientific evidence). These treatment recommendations encompassed choice of agent, dose to be used and duration of treatment. The working group convened in May 2019 and November 2019 to review the treatment recommendations from each subgroup and reach consensus. A nominal group technique was used to come to consensus, and recommendations achieving >80% agreement (10 of 12 working group members) were considered to reach consensus [23]. If consensus was not reached, the recommendation was revised, and the working group repeated the voting until consensus was achieved. The recommendations were graded as either strong or weak according to the level of evidence. Recommendations graded as strong were based on good-quality clinical trial evidence, and recommendations graded as weak were based on expert consensus and anecdotal/observational clinical practice.

This article was developed by collating the consensus recommendations agreed upon by the working group, and circulating the draft document to the working group members for critical review.

3. Microbiology and diagnostics

The availability of diagnostic tools and laboratory resources for analysis of MDR pathogens varies across Arab countries of the Middle East. The gold standard for diagnosing MDR pathogens is based on culture (phenotyping) methods, preferably combined with rapid commercial molecular (genotyping) assays which have higher sensitivity and specificity, and accelerate the detection of MDR organisms to guide directed therapy and infection control practices [24,25].

Immunochromatographic assays could be useful as a rapid and inexpensive method for countries with a high prevalence of OXA-48 [26]. Broth microdilution is recommended by the Clinical and Laboratory Standards Institute and the European Committee on Antimicrobial Susceptibility Testing for colistin minimum inhibitory concentration (MIC) testing [27].

4. Empiric therapy

Empiric antibiotic therapy, before the results of antimicrobial susceptibility testing are available, should be selected based on local epidemiology and susceptibility patterns. If combination empiric therapy is used, two agents with different mechanisms of action should be selected. The choice of agents for empiric therapy depends on the site and severity of the infection, prior colonization and previous infection, patient history of allergy, and antimicrobials available on hospital formularies.

Consideration for empiric antibiotic therapy typically incorporates risk stratification. The most common risk factors for MDR infections include: advanced age; immunosuppressed state; intensive care unit (ICU) admission; polytrauma; prolonged use of broad-spectrum antibiotics; invasive instrumentation (e.g. central venous catheter, endotracheal intubation); colonization of respiratory, gastrointestinal or urinary tract; post-surgery; antibiotic use in preceding year; inappropriate antibiotic use; and referral from a long-term care facility [28–36].

In some hospitals, initiation of empiric antibiotic therapy may be restricted to specified cut-off points of AMR according to the annual antibiogram.

5. Recommendations for directed therapy

Once the results of antimicrobial susceptibility testing are available, a regimen can be chosen from the active agents. Other considerations in the selection of a regimen include patient drug allergies or intolerance, renal or hepatic impairment, the need to cover additional infections, and hospital formulary. Treatment should be individualized, and consultation with an expert in the management of MDR infections is strongly advised. Involvement of a multidisciplinary antimicrobial stewardship team, including infectious disease, microbiology and clinical pharmacy specialists, is recommended. Adequate management of infections also includes source control and removal of associated foreign material, such as urinary or venous catheters. Where bacteraemia is believed to be associated with central lines, and line removal is not possible, antibiotic lock therapy is recommended in addition to the use of intravenous antibiotics in order to increase the likelihood of clearing the bacteria [37]. Continued monitoring of the patient for clinical worsening following initial improvement is important. Emergent resistance to antibiotics during therapy can occur, and it may be necessary to change therapy according to new susceptibility testing results.

Consensus recommendations for directed treatment are presented in Tables 1–4. First-choice therapies are those with the strongest supporting evidence for the specific infection. Alternative choices are recommended when the first choice is not available or not feasible due to intolerance, cost or availability. All antibiotics recommended for treatment are to be used intravenously, unless stated otherwise, and should be used where susceptible organisms are identified. All agents are listed in alphabetical order unless there is specific evidence favouring one regimen over another. Where guidelines have been provided for treatment duration, it should be noted that all therapy should be individualized according to the characteristics of the patient and the underlying condition.

Doses for suggested agents are listed in Table 5 and are based on the treatment of adults with normal renal function.

Table 1
Directed treatment for *Acinetobacter baumannii* infections.

	Bacteraemia and nosocomial pneumonia	cUTI and cSSTI
First-choice therapy for *A. baumannii* infections	Colistin [IV and inhaled (nebulized[a]) for patients with pneumonia] or polymyxin B[b] monotherapy in stable patients *[Weak]* Colistin [IV and inhaled (nebulized[a]) for patients with pneumonia] or polymyxin B[b] in combination with one of the following in critically ill patients: *[Weak]* – Aminoglycoside (for bacteraemia only)[c] – Ampicillin/sulbactam[b] – Carbapenem (high-dose, extended infusion)[d] – Fosfomycin[e] – Minocycline[b] – Rifampicin[f] – Tigecycline (high-dose)	Monotherapy with one of the following: *[Weak]* – Aminoglycoside[c] – Ampicillin/sulbactam – Carbapenem (high-dose, extended infusion)[d] – Colistin – Doxycycline (for cSSTI only) – Fosfomycin (for cUTI only) – Tigecycline (for cSSTI only; consider combination therapy with antibiotics, if needed) – Trimethoprim-sulfamethoxazole
Duration	7–14 days[g]	cUTI: 7 days[g] cSSTI: 7–14 days[g]
Treatment notes	Bacteraemia: intravascular catheter or other devices should be removed Pneumonia: IV colistin yields low concentration in the lung; supplement with inhaled colistin but consider risk of bronchospasm	cUTI: Urinary catheter or other devices should be removed cSSTI: Debridement of affected tissue may be necessary; ensure tissue sample is collected after debridement; superficial swabs are not recommended

cUTI, complicated urinary tract infection; cSSTI, complicated skin and soft tissue infection; IV, intravenous.
[a] For nebulized therapy, a vibrating plate nebulizer may be preferred. Prepare immediately prior to administration to avoid potential lung toxicity. Consider use of a bronchodilator (e.g. albuterol) 15 min before use. If a patient is on a ventilator, place medicine in a T-piece at the mid-inspiratory circuit of the ventilator.
[b] Not available in all countries.
[c] Should only be used in desperate measures and renal function should be monitored due to the risk of nephrotoxicity with combined therapy.
[d] Not recommended if carbapenem minimum inhibitory concentration >16 against *A. baumannii.*
[e] Testing is not available in some institutions.
[f] Use of rifampicin is limited by its inclusion in tuberculosis treatment protocols, but it may be useful in patients who cannot have lines removed or changed. Should be avoided where other options are available.
[g] Treatment duration to be individualized according to the underlying condition.

Table 2
Directed treatment for *Pseudomonas aeruginosa* infections.

	Bacteraemia[a] and nosocomial pneumonia[a]	cUTI[a] and cSSTI[a]
First-choice therapy for *P. aeruginosa* infections	Carbapenem (except ertapenem) with one of the following: *[Strong]* – Aminoglycoside – Fosfomycin Ceftazidime/avibactam Ceftolozane/tazobactam Piperacillin/tazobactam with or without: – Aminoglycoside – Colistin (IV and inhaled for pneumonia) – Fosfomycin	cUTI or cSSTI: *[Strong]* Ceftazidime/avibactam Ceftolozane/tazobactam cUTI alone: *[Weak]* Aminoglycoside Aztreonam[b] Carbapenem (except ertapenem) with one of the following: – Aminoglycoside – Fosfomycin Piperacillin/tazobactam in combination with one of the following: – Aminoglycoside – Colistin – Fosfomycin
Alternative therapy	Aztreonam[b] + additional active agent *in vitro [Weak]* Colistin (IV and inhaled for pneumonia) + fosfomycin *[Weak]*	cUTI: colistin + fosfomycin *[Weak]* cSSTI: fosfomycin[d] in combination with one of the following: *[Weak]* – Aminoglycoside – Antipseudomonal quinolone – Colistin
Duration	7–14 days[c]	cUTI: 7–14 days[e] cSSTI: dependent on debridement and clinical response
Treatment notes	Bacteraemia: intravascular catheter or other devices should be removed Pneumonia: IV colistin yields low concentration in the lung; supplement with inhaled colistin but consider risk of bronchospasm	cUTI: urinary catheter or other devices should be removed cSSTI: debridement of affected tissue may be necessary; ensure tissue sample is collected after debridement; superficial swabs are not recommended

cSSTI, complicated skin and soft tissue infection; cUTI, complicated urinary tract infection; IV, intravenous.
[a] In cases of severe infections, high risk of death, septic shock or neutropenia, initial therapy used in combination with aminoglycoside OR antipseudomonal quinolone (if susceptible) is indicated while bacterial burden is high and until septic shock resolves.
[b] Aztreonam as a monobactam with special activity against MBLs such as NDM-1-producing pseudomonas can be considered if proven susceptible, particularly in cases of penicillin allergy.
[c] Treatment duration to be individualized according to the underlying condition.
[d] Data show that fosfomycin has good penetration in the bone.
[e] Treatment duration to be individualized according to the underlying condition; in special circumstances, such as patients undergoing kidney transplant, the duration may be extended to ≥21 days.

Table 3
Directed treatment for carbapenem-resistant Enterobacteriaceae (CRE) infections.

	Bacteraemia and nosocomial pneumonia		cUTI and cSSTI	
First-choice therapy for Enterobacteriaceae (CRE) infections	KPC + OXA-48	Ceftazidime/avibactam alone in stable patients *[Strong]* Ceftazidime/avibactam in combination with one of the following for critically ill patients: *[Strong]* – Aminoglycoside – Colistin – Fosfomycin	KPC + OXA-48 (cUTI)	Ceftazidime/avibactam *[Strong]*
	NDM-1 + OXA-48 MBL (e.g. NDM-1)	Ceftazidime/avibactam in combination with aztreonam *[Weak]* Colistin (IV and inhaled for pneumonia) in combination with one or both of the following: *[Strong]* – Fosfomycin – Tigecycline – Any other in-vitro active agent	cSSTI	Tigecycline *[Strong]* Ceftazidime/avibactam (except for treatment of MBL) *[Strong]*
Alternative therapy	Meropenem MIC ≤16	High-dose meropenem in combination with one of: *[Weak]* – Aminoglycoside – Colistin (IV and inhaled for pneumonia) – With or without high-dose tigecycline	KPC and OXA-48 and meropenem MIC ≤16	High-dose meropenem in combination with one of the following: *[Weak]* – Aminoglycoside – Colistin – Fosfomycin
	Meropenem MIC >16	Colistin (IV and inhaled for pneumonia) in combination with high-dose tigecycline with/without one of: *[Weak]* – Aminoglycoside – Fosfomycin	MBL (e.g. NDM-1) and/or meropenem MIC >16	Monotherapy *[Strong]* – Aminoglycoside – Colistin – Fosfomycin
			cSSTI	Monotherapy with one of the following: *[Weak]* – Colistin – Trimethoprim/sulfamethoxazole Consider combination therapy if clinically indicated
Duration	8–14 days[a,b]		cUTI: 7–14 days[a] cSSTI: 5–7 days[a]	
Treatment notes			cUTI: source control is mandatory; urinary catheter or other devices should be removed	

cSSTI, complicated skin and soft tissue infection; cUTI, complicated urinary tract infection; IV, intravenous; KPC, *Klebsiella pneumoniae* carbapenemase; MBL, metallo-beta-lactamase; MIC, minimum inhibitory concentration.
[a] Treatment duration to be individualized according to the underlying condition (e.g. longer treatment in neutropenic or immunocompromised patients).
[b] For patients with bacteraemia, treatment can be discontinued after 48 h in immunocompetent patients if afebrile and following normalization of sepsis markers.

The importance of appropriate dosing cannot be overstated to attain optimal efficacy and prevent the development of resistance [38,39]. Dose selection should always consider the unique pharmacokinetic/pharmacodynamic (PK/PD) characteristics of the chosen agent, the patient's physiology and underlying comorbidity, and the target pathogen [40]. Strategies to achieve improved antimicrobial exposure include adequate loading doses, extended/continuous infusions and therapeutic drug monitoring (TDM) [40]. While PK/PD ratios provide the clinician with an appropriate target to guide antimicrobial dosing, the exact PK/PD target in plasma for a specific antibiotic varies with the pathogen and site of infection [39]. TDM using varying practices is widely available for aminoglycosides and is becoming increasingly common for beta-lactams, particularly piperacillin and meropenem [39]. The clinical feasibility of TDM for colistin is limited by complicated laboratory analytical methods, and TDM for other drug classes is not currently widespread [39]. Alternative approaches to optimize dosing include population-based PK/PD models, nomograms, and computer software using Bayesian forecasting [38,41].

Individualized dosing using PK/PD variables is of particular relevance in critically ill patients with sepsis, septic shock, severe trauma or burns injury, major surgery, febrile neutropenia, cystic fibrosis, organ dysfunction and obesity [38]. Augmented renal clearance has been reported in up to 65% of critically ill patients with normal renal function over the first 7 days in ICU [42]. Enhanced renal elimination may result in subtherapeutic antibiotic concentrations, which can lead to treatment failure and a greater risk of antibiotic resistance [43]. Individualized dosing in critically ill patients should include consideration of augmented renal clearance, which can be identified by daily measurement of creatinine clearance, and toxicity due to drug accumulation in the event of acute kidney injury [42,43].

5.1. *Acinetobacter baumannii*

Evidence for the use of different antimicrobials for the treatment of *A. baumannii* infections is primarily based on in-vitro data and observational series [44]. Trials that have evaluated the efficacy and safety of different antimicrobial regimens for *A. baumannii* infections are limited by their small sample sizes, variability in the severity of disease and patient comorbidities, and lack of a comparator group [44]. In the setting of resistance to cephalosporins, fluoroquinolones and carbapenems, therapeutic options are limited. Polymyxins are the main therapeutic option, but these should not be used as monotherapy in critically ill patients (e.g. patients with sepsis and associated organ dysfunction) as resistance can develop during therapy [44]. Management of patients with MDR *A. baumannii* infections should be done in consultation with an infectious disease expert whenever possible.

Table 4
Directed treatment for extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae infections.

	Bacteraemia[a] and nosocomial pneumonia	cUTI	cSSTI	cIAI
First-choice therapy for Enterobacteriaceae (ESBL) infections	Monotherapy with one of the following: [Strong] – Carbapenem (ertapenem is preferred; for pneumonia, doripenem should be avoided as not approved by US FDA for VAP) – Ceftazidime/avibactam – Ceftolozane/tazobactam (consider high-dose therapy)	Monotherapy with one of the following: [Strong] – Carbapenem[b] – Ceftazidime/avibactam – Ceftolozane/tazobactam – Fosfomycin	– Carbapenem – Tigecycline	– Carbapenem – Ceftazidime/avibactam + metronidazole – Ceftolozane/tazobactam + metronidazole – Tigecycline
Alternative therapy	For bacteraemia: [Weak] – Piperacillin/tazobactam (extended infusion every 6 h) in combination with aminoglycoside For nosocomial pneumonia: [Weak] monotherapy with one of the following: – Piperacillin/tazobactam – Tigecycline (high-dose)	Monotherapy with one of the following: [Strong] – Aminoglycoside – Piperacillin/tazobactam – Quinolone – Trimethoprim/sulfamethoxazole	– Ceftazidime/avibactam – Ceftolozane/tazobactam – Piperacillin/tazobactam[c] – Quinolone – Trimethoprim/sulfamethoxazole	– Piperacillin/tazobactam [Weak]
Duration	7–10 days[d]	7–10 days[e]		5–10 days[e]
Treatment notes	For bacteraemia: intravascular catheter or other devices should be removed			

cIAI, complicated intra-abdominal infection; cSSTI, complicated skin and soft tissue infection; cUTI, complicated urinary tract infection; MIC, minimum inhibitory concentration; VAP, ventilator-associated pneumonia; FDA, Food and Drug Administration.
[a] No data in primary bacteraemia, so data extrapolated from data in secondary infections.
[b] Ertapenem preferred except for cases of prostatitis.
[c] Piperacillin/tazobactam may be considered in stable patients if susceptible; use high-dose piperacillin/tazobactam if MIC=4–8.
[d] Seven days if source is controlled; treatment duration to be individualized according to the underlying condition.
[e] Treatment duration to be individualized according to the underlying condition.

Consensus recommendations for the treatment of MDR *A. baumannii* infections resistant to cephalosporins, fluoroquinolones and carbapenems are listed in Table 1.

5.1.1. Acinetobacter baumannii bacteraemia

A. baumannii bloodstream infections with drug-resistant isolates are associated with poor outcomes regardless of therapy [44]. Recommended first-choice agents are colistin or polymyxin B (where available) as monotherapy in stable patients, or in combination with other antibiotics in critically ill patients. Available evidence suggests that monotherapy is as effective as combination therapy in terms of mortality outcomes [45], although colistin combination therapy may be associated with improved eradication rates compared with monotherapy in patients with extremely-drug-resistant isolates [46–48]. Note that tigecycline enters tissues rapidly after intravenous administration, resulting in low serum levels, so it should not be used alone for *A. baumannii* bacteraemia [49]. It should also be noted that carbapenems are not recommended if the MIC against *A. baumannii* is >16 [50,51].

5.1.2. Acinetobacter baumannii nosocomial pneumonia

Pneumonia due to CRAB is, by definition, a serious infection. Treatment recommendations are based on the findings of published studies suggesting the value of colistin in treating these infections [52–58] and expert consensus. Intravenous colistin and adjunctive inhaled colistin is recommended as intravenous colistin yields a low lung concentration [59]; the additional benefits of inhaled colistin outweigh the potential risk of bronchoconstriction [44,60]. Polymyxin B is an alternative to colistin and may be used alone or in combination with other agents, depending on patient stability.

5.1.3. Acinetobacter baumannii UTIs

A. baumannii colonizes the urinary tract readily, particularly in the presence of an indwelling catheter; therefore, it is important to check for pyuria and rule out other sources of infection contributing to the clinical presentation as it can merely represent asymptomatic bacteriuria [44]. Recommendations for monotherapy are extrapolated from data on *A. baumannii* treatment of other sites, as there is a paucity of data on UTIs in this context.

5.1.4. Acinetobacter baumannii cSSTIs

Monotherapy is generally considered sufficient for *A. baumannii* cSSTIs, although combination of antibiotics with tigecycline may be considered when necessary. Tigecycline achieves high concentrations in tissue sites, and achieves favourable response rates in patients with *A. baumannii* cSSTIs with a high severity of illness [61].

5.2. Pseudomonas aeruginosa

There are no convincing clinical data for the treatment of infections due to MDR *P. aeruginosa* that demonstrate improved outcomes with combination therapy over monotherapy [62]. However, initiation of a second antipseudomonal agent should be considered in severe infections, infections that are slow to respond or fail to respond to a single active agent, and in certain high-risk patients such as those with neutropenia [62]. Clinical evidence for combination antibiotic strategies for MDR *P. aeruginosa* are limited because of the paucity of well-controlled comparative trials using clinically important endpoints [62]. If combination therapy is used, it should be done in consultation with an infectious disease expert whenever possible.

Consensus recommendations for the treatment of MDR *P. aeruginosa* infections are listed in Table 2.

Table 5
Recommended doses of antibiotics used for the treatment of multi-drug-resistant infections in adults with normal renal function[a]

Class/agent	Dose
Advanced beta-lactamase inhibitor combinations	
Ceftazidime/avibactam	2.5 g intravenously every 8 h
Ceftolozane/tazobactam	1.5 g intravenously every 8 h (3 g intravenously every 8 h for pneumonia)
Aminoglycosides[b]	
Amikacin	15–25 mg/kg intravenously every 24 h
Gentamicin	5–7 mg/kg intravenously every 24 h
Rifampicin	600 or 900 mg once daily (orally or intravenously)
Plazomicin	15 mg/kg intravenously every 24 h
Tobramycin	5–7 mg/kg intravenously every 24 h
Antipseudomonal penicillins + beta-lactamase inhibitors	
Piperacillin/tazobactam	3.375 g intravenously infused over 4 h every 8 h OR 4.5 g intravenously every 6 h
Carbapenems[c]	
Doripenem	0.5 g intravenously every 8 h
Ertapenem	1 g daily intravenously infused over 0.5 h (or intramuscularly)
Imipenem	0.5–1 g intravenously every 6 h or 1 g intravenously every 8 h
Meropenem	1–2 g intravenously every 8 h
Fluoroquinolones[d]	
Ciprofloxacin	400 mg intravenously every 8 h (orally or intravenously)
Levofloxacin	750 mg once daily or 500 mg every 12 h (orally or intravenously)
Folate pathway inhibitors	
Trimethoprim/sulfamethoxazole	15–20 mg/kg intravenously divided into three to four doses
Glycylcyclines	
Tigecycline[e]	100 mg intravenous loading dose, followed by 50 mg intravenously every 12 h
Monobactams	
Aztreonam	2 g intravenously every 8 h
Penicillins + beta-lactamase inhibitors	
Ampicillin/sulbactam	3 g intravenously every 6 h
Phosphonic acids	
Fosfomycin	4–6 g intravenously every 6 h
Polymyxins	
Colistin	~9 million IU intravenous loading dose infused over 0.5–1 h then a daily intravenous dose ~9–10.9 million IU divided into two and infused over 0.5–1 h every 12 h Nebulized dose 2.25–4.5 million IU twice daily, up to 5 million every 8 h
Tetracyclines	
Doxycycline	200 mg once daily OR 100 mg twice daily (orally or intravenously)

[a] Individualized dosing using pharmacokinetic/pharmacodynamic variables is recommended, particularly to account for changes in renal function. In addition, consider augmented renal clearance in ICU patients.
[b] Aminoglycosides are generally used in combination with another agent and should NOT be used as monotherapy for infections other than those of the lower urinary tract.
[c] High-dose carbapenems are typically twice the standard dose; for example, high-dose ertapenem can be given as 1 g every 12 h or 500 mg every 6 h; high-dose meropenem can be given as 2 g infused over 3–4 h every 8 h.
[d] Fluoroquinolones are the only class of antibiotics with antipseudomonal activity that have an oral formulation.
[e] Tigecycline may not reach adequate levels in the serum, urinary tract or central nervous system to successfully treat infections in these organ systems; use high-dose tigecycline (200 mg loading dose then 100 mg every 12 h) in serious infections.

5.2.1. Pseudomonas aeruginosa bacteraemia

Many patients with *P. aeruginosa* bacteraemia have an identifiable focus of infection at the time of initial evaluation, but the source remains unknown in up to 40% of cases [63,64]. The most common sources of *P. aeruginosa* bacteraemia are respiratory (25%) and urinary tract (19%), followed by central line and skin and soft tissues [63]. Although carbapenems (except ertapenem) may be used as part of combination therapy, treatment with ceftazidime/avibactam, ceftolozane/tazobactam or piperacillin/tazobactam with or without additional agents may be preferable in *P. aeruginosa* resistant to carbapenem. Several studies support the use of colistin in the management of MDR *P. aeruginosa* infections in this context [65–67]. The duration of treatment is largely dictated by the primary site of infection. In bacteraemia secondary to a central line in a non-neutropenic host, treatment can be stopped after 7 days once the catheter has been removed and the patient has responded adequately.

5.2.2. Pseudomonas aeruginosa nosocomial pneumonia

P. aeruginosa is one of the leading causes of nosocomial pneumonia [68]. Therapeutic options are identical to those for *P. aeruginosa* bacteraemia. Inhaled colistin may be considered as adjunctive to intravenous therapy in MDR infection [68]. Aminoglycosides should not be used as monotherapy because success rates are low, and the increased risk of nephrotoxicity or ototoxicity resulting from the high serum concentrations required for adequate penetration into the lung makes them an unattractive option [68].

5.2.3. Pseudomonas aeruginosa UTIs

Patients with *P. aeruginosa* causing UTI are more likely to have a chronic underlying disease, and often present with healthcare-associated infection and a recent urinary tract instrumentation and/or chronic indwelling urinary catheter [69]. Standard of care consists of elimination of the predisposing condition, when possible, in combination with antibiotic therapy that is generally considered adequate for treatment in the absence of septic shock [68].

5.2.4. Pseudomonas aeruginosa cSSTIs

P. aeruginosa is one of the most common Gram-negative pathogens isolated from cellulitis in patients with neutropenia, surgical site infections, infections following trauma, or infections of chronic decubitus ulcers [50]. Among cSSTIs due to *P. aeruginosa*, two clinical syndromes need special consideration: ecthyma gangrenosum and burn wound infections. Surgery is not always warranted, but debridement may be required in patients with extensive necrosis and infected eschar [50]. In all cases, the importance of antimicrobial therapy is unquestioned and is dependent on susceptibility testing. The usual duration of antibiotic therapy is 10–

14 days, but shorter courses may be considered in patients who have adequate source control with prompt resolution of clinical signs and symptoms.

5.3. Carbapenem-resistant Enterobacteriaceae

CRE are classified as Class A (e.g. KPC), Class B (e.g. NDM-1) and Class D (e.g. OXA). Classes A and D have a serine-based hydrolytic mechanism, while Class B consists of metallo-beta-lactamase (MBL). In addition, there are CREs due to mechanisms other than carbapenemase production [70].

Therapeutic options for carbapenemase-producing Enterobacteriaceae are limited, and no single antibiotic regimen has been clearly defined to be superior over another [71]. The rationale for using two or more agents includes the high mortality associated with serious CRE infections, emerging resistance during monotherapy, and the deficiency of effective single-drug alternatives. Several observational studies and a systematic review have suggested that combination therapy may offer a survival advantage in severely ill patients [72–74]. This includes studies on the use of ceftazidime/avibactam in Gram-negative pathogens with resistance to carbapenem or multiple drugs [75,76].

Using molecular diagnostic techniques to determine the type of the isolated carbapenemase not only guides the best therapeutic option, but also enables de-escalation and antimicrobial stewardship as acquired resistance to novel beta-lactam/beta-lactamase inhibitors has been reported previously [77,78]. Management of patients with CRE infections should be based on the results of susceptibility testing, and done in consultation with an infectious disease expert whenever possible.

Consensus recommendations for the treatment of CRE infections are listed in Table 3.

5.3.1. CRE bacteraemia

Evidence from observational studies suggests that combination therapy is associated with reduced mortality in severe CRE bacteraemia [71], and that heterogeneous regimens are favourable in this patient group [77,79–81]. Combination therapy may be used to delay the emergence of resistance.

The use of ceftazidime/avibactam is supported in the literature [82–84] as it has good activity against KPC and OXA-48 but poor activity against NDM-1 and NDM-1/OXA-48 [71]. For treatment of NDM-1- and OXA-48-producing Enterobacteriaceae, ceftazidime/avibactam should be combined with aztreonam [71]. Regimens containing ceftazidime/avibactam have been superior in treating KPC-producing Enterobacteriaceae bacteraemia [75,76]. Aztreonam is effective against both NDM-1- and OXA-48-producing Enterobacteriaceae [82]. For KPC, if meropenem MIC $\leq$16, salvage therapy may be considered with high-dose meropenem in combination with other active agents.

5.3.2. CRE nosocomial pneumonia

Recommendations for the management of CRE nosocomial pneumonia are identical to the recommendations for the management of CRE bacteraemia [71]. The only difference between these infection sites is that inhaled colistin may be used in combination with intravenous colistin to ensure adequate tissue penetration in nosocomial pneumonia [85]. As with the treatment of CRE bacteraemia, high-dose meropenem in combination with other active agents may be used for salvage therapy for KPC if meropenem MIC $\leq$16, when no other options are available.

5.3.3. CRE UTIs

UTIs secondary to CRE have been on the rise globally and regionally; drugs with high urinary concentrations should always be used to achieve maximum success rates. Currently available options are limited and include ceftazidime/avibactam [86] and high-dose meropenem as part of combination therapy in MBL, or monotherapy when meropenem MIC <16 [71]. Of note, fosfomycin remains active against several CREs and has been used in intravenous formulations in clinical studies [87,88]. Due to rapid development of fosfomycin resistance if used as monotherapy, fosfomycin should always be used in combination with another active agent.

5.3.4. CRE cSSTIs

Tigecycline or ceftazidime/avibactam should be considered as first-choice treatment options for CRE cSSTIs [70]. Colistin or trimethoprim/sulfamethoxazole monotherapy or in combination with other agents may be considered as alternatives.

5.4. ESBL-producing Enterobacteriaceae

Carbapenems are the most established therapeutic option for severe infections caused by ESBL-producing Enterobacteriaceae [89]. However, carbapenem-sparing strategies should be considered to prevent selection of carbapenemase-producing Enterobacteriaceae. The novel beta-lactam/beta-lactamase inhibitors compare favourably with carbapenems [89]. Failure to treat with an antibiotic active against ESBL-producing strains is associated with higher mortality [90]. The susceptibility of ESBLs to beta-lactamase inhibitors has decreased, mainly due to excessive use of these agents [90]. Management of patients with infections caused by ESBL-producing Enterobacteriaceae should be done in consultation with an infectious disease expert whenever possible.

Consensus recommendations for the treatment of infections caused by ESBL-producing Enterobacteriaceae are listed in Table 4.

5.4.1. ESBL bacteraemia

First-choice management of ESBL bacteraemia with carbapenem, ceftazidime/avibactam or ceftolozane/tazobactam should be considered. Data from the study by Gutiérrez-Gutiérrez et al. [91] suggest that ertapenem should be preferred over other carbapenems in order to avoid over-use of antipseudomonal carbapenems.

Ceftolozane/tazobactam exhibits excellent in-vitro activity against ESBL-producing Enterobacteriaceae isolated from bloodstream infections [90].

Piperacillin/tazobactam has good in-vitro activity against ESBL-producing organisms but with controversial clinical efficacy. Treatment failures have been described with piperacillin/tazobactam due to high inoculum effect [90]. Piperacillin/tazobactam alone was found to be inferior to carbapenem for the treatment of bacteraemia in the MERINO trial [92]. Piperacillin/tazobactam in combination with an aminoglycoside may be considered as an alternative therapy for ESBL bacteraemia.

Available data do not support the use of cefepime for severe ESBL infections or those with high MICs [93].

5.4.2. ESBL nosocomial pneumonia

Hospital-acquired pneumonia secondary to ESBL-Enterobacteriaceae is a very common nosocomial infection, with variable rates in the region secondary to *K. pneumonia* or *E. coli* in the majority of cases. These organisms, by definition, are resistant to broad-spectrum cephalosporins, and carbapenems (ertapenem as a preference [94]) are usually considered to be the drug of choice, particularly when managing severe infections [89]. Ceftazidime/avibactam and high-dose ceftolozane/tazobactam are efficacious alternatives to carbapenem [89]. Monotherapy with piperacillin/tazobactam or high-dose tigecycline may be considered [89]. The working group rejected the inclusion of quinolones as an alternative therapy in patients who are susceptible and not critically ill (only 75% agreed upon inclusion in the treatment recommendations); quinolones may be widely used in practice, but this is not supported by the available evidence.

Treatment duration as per most recent recommendations is 7–10 days for the majority of cases. A longer treatment course may be justified when managing heavily immunocompromised hosts with severe pneumonia, and in selected patients with severe pyogenic complications such as empyema or lung abscess [85].

5.4.3. ESBL UTIs

UTIs secondary to ESBL-Enterobacteriaceae rank high among all nosocomial infections, and carbapenems are the cornerstone for managing these infections, with a preference for ertapenem except in cases of prostatitis [95]. Ceftazidime/avibactam and ceftolozane/tazobactam have been approved by the US Food and Drug Administration (FDA) for the treatment of complicated UTIs secondary to MDR Gram-negative bacteria. These beta-lactamase inhibitor combinations have high success rates and have proven to be cost-effective as monotherapy when managing UTIs secondary to ESBL-Enterobacteriaceae [86,96,97]. Monotherapy with piperacillin/tazobactam and quinolones as alternatives are also justified in the literature [98–100], and aminoglycoside, plazomicin or trimethoprim/sulfamethoxazole monotherapy may also be considered.

5.4.4. ESBL cSSTIs

Carbapenems or tigecycline are the first-choice agents for the management of ESBL cSSTIs [61,89]. However, it is advisable to use carbapenem-sparing tactics to reduce resistance emerging from their excess use. Ceftazidime/avibactam and ceftolozane/tazobactam represent valuable alternatives, but their role relies on MIC testing and detection of resistance genes. The duration of therapy is preferably 7–10 days; however, the duration of treatment should be based on the patient's clinical condition, surgical debridement and clinical response.

5.4.5. ESBL cIAIs

The use of carbapenem or tigecycline monotherapy is recommended, while studies also suggest the efficacy of combination therapy with ceftazidime/avibactam plus metronidazole [96,101] or ceftolozane/tazobactam plus metronidazole [102]. The duration of antimicrobial therapy for ESBL cIAIs can be limited to 5 days when adequate source control has been achieved and contaminated material has been cleared from the intra-abdominal space [103]. Longer courses of antibiotic therapy are appropriate in patients with suboptimal source control, or when an indwelling catheter is required for ongoing drainage [103].

6. Discussion and conclusions

These consensus recommendations take into consideration the diverse social and healthcare structures among the Arab countries of the Middle East, and cover a gap not provided by international guidelines. Specifically, these recommendations list several treatment options per condition per pathogen to accommodate variations in the availability of medications and diagnostic technologies between countries in the region. As a result, some recommendations may include off-label use of certain antibiotics for some countries.

It is important to note that these recommendations are based on expert opinion after review of the literature, consideration of combined clinical experience and observation of patient outcomes in clinical practice. They are not intended to replace internationally recognized practice guidelines, but instead add insight from local experts to provide a regional context so clinicians can interpret and best apply guidelines using the resources available in their healthcare settings.

These recommendations are not exhaustive and focus on the top MDR pathogens of concern in the region, as identified by the working group, and also reflect the WHO critical priority Gram-negative pathogens. There are wide-varying differences in AMR rates within the region, but this is not surprising given the geographical spread, distinct population types, different climates and diverse socio-economic groups among the Arab countries of the Middle East [1].

The difference in resistance trends across Arab countries in the Middle East underscores the importance of initiating a structured and standardized surveillance system as recommended by WHO in 2015 with the Global Antimicrobial Resistance Surveillance System (GLASS) initiative [28]. As of February 2020, all but three Arab countries in the Middle East had enrolled in the GLASS initiative, but because countries are at different stages of development of their surveillance systems, prevalence data for MDR pathogens are not yet available for all countries [2].

Heavy international travel occurs in the region due to the large population of expatriates and the annual pilgrimage to the holy city of Mecca. Travel is a known risk factor for acquiring and transmitting infectious diseases, including those caused by antibiotic-resistant bacteria [104]. A recent study showed that returning travellers from Hajj acquired MDR *A. baumannii* and NDM-producing *E. coli* during the pilgrimage [7]. In addition, epidoses of septicaemia increased during Hajj due to the influx of international patients [7].

The ongoing civil war in Syria, as well as other conflicts and instability in areas of the Middle East, have resulted in an abundance of refugees and migrants [105]. Carriage of MDR pathogens is frequent in refugees and migrants, and transmission is facilitated by collapsed infrastructures and poor hygiene conditions in their countries of origin and along the immigration route [105]. Refugees may serve as vehicles for dissemination of novel AMR mechanisms in non- or low-endemic countries [106]. Moreover, wide use of antimicrobial drugs in the management of war-related injuries contributes to the increase in MDR pathogens [107]. Gram-negative pathogens are predominant in later stages of war-related wound infections [107], and a regional perspective of MDR epidemiology and treatment recommendations may facilitate appropriate use of antimicrobial therapy in these patients.

Epidemiological variations across the region necessitate careful consideration of the local epidemiology of infections caused by MDR Gram-negative pathogens, as well as the antibiogram at the level of the country, the state, the hospital and, at times, the individual hospital unit. Unfortunately, published national data are lacking for the region. Enhancements to AMR surveillance should be planned and supported by information technology that allows record linkage and simplification of surveillance from the laboratory to the national and regional level. It is expected that shared regional data will, one day, become a reality with the GLASS initiative and ongoing support from the WHO Eastern Mediterranean Regional Office.

The availability of new antimicrobial agents will be welcomed in the region, but cost and access are critical limiting factors. Not all antimicrobials available in regions such as North America and Europe are available in the Middle East, and supply issues can be problematic in some countries. These recommendations list several treatment options, where possible, to account for these issues. Meropenem/vaborbactam and cefiderocol are newer agents that have been approved for use by the US FDA but may have low availability in the region. Meropenem/vaborbactam only has activity against KPC beta-lactamases, while cefiderocol has activity against all classes of CRE and *A. baumannii* [108,109]. These agents may be considered as alternative treatment options.

It is hoped that these consensus recommendations will be used to help direct and formulate antimicrobial policies to aid the prescribing practice of infectious disease specialists and other clinicians. It is recognized that antimicrobial budgets and the cost of new antimicrobials factor in the choice of therapy, but recommendations for first-choice agents were determined primarily on the basis of therapeutic efficacy and safety rather than cost. De-escalation strategies also need to be considered, but were beyond the scope of these recommendations.

The value of a high-quality laboratory, skilled multi-disciplinary team, robust antibiotic stewardship policy, and effective infection prevention and control practices cannot be overstated in the management of MDR Gram-negative infections. Optimization of available antimicrobial therapy regimens by selection of the most appropriate agent or combination and effective dosing regimens is critical.

The authors aim to review and update these recommendations periodically as treatment strategies for the management of MDR Gram-negative bacteria evolve, with new or revisited therapeutic options, emerging mechanisms of resistance and changing resistance patterns.

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