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Phenotypic and genotypic characterisation of cephalosporin-, carbapenem- and colistin-resistant Gram-negative bacterial pathogens in Lebanon, Jordan and Iraq



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ABSTRACT

Antimicrobial resistance (AMR) is a worldwide health concern that continues to escalate. A PubMed literature search identified articles from January 2015–August 2020 reviewing cephalosporin-, carbapenem- and colistin-resistant Gram-negative bacteria (GNB) in Lebanon, Jordan and Iraq, specifically focused on three main pathogens, namely *Acinetobacter* spp., Enterobacteriaceae (i.e. *Escherichia coli* and *Klebsiella* spp.) and *Pseudomonas aeruginosa*. Sixty-seven relevant articles published within the past 5 years highlighting trends in AMR in Lebanon, Jordan and Iraq were included. Increased resistance to carbapenems in *Acinetobacter* spp. isolates was observed in Lebanon, Jordan and Iraq; colistin resistance remained relatively low. Studies on Enterobacteriaceae isolates were more varied, with high rates of carbapenem and cephalosporin resistance and lower levels of colistin resistance in Lebanon. Studies from Iraq found high cephalosporin and colistin resistance along with increased susceptibility to carbapenems. In Jordan, most studies recorded high resistance to cephalosporins along with high susceptibility to carbapenems and colistin. Studies on *P. aeruginosa* isolates were limited: most isolates in Lebanon were carbapenem-resistant and colistin-susceptible; studies in Iraq showed varying levels of resistance to carbapenems and cephalosporins with high susceptibility to colistin; and studies in Jordan found varying levels of susceptibility to carbapenems, cephalosporins and colistin. The most commonly observed resistance mechanisms in GNB were genetic modifications causing increased expression of antimicrobial-inactivating enzymes and decreased permeability. Overall, this review highlights the concerning rise in AMR and the need for improved understanding of the resistance mechanisms to better inform healthcare providers when recommending treatment for patients in this region.

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1. Introduction

Antimicrobial resistance (AMR) represents a global public-health threat [1]. Over time, pathogens resistant to clinically relevant antimicrobial agents have steadily emerged and evolved to cause life-threatening infections among critically-ill patients [2–5].

Globally, AMR is estimated to cause approximately 700 000 deaths annually, with a projected estimate of 10 million deaths in 2050, and is of particular concern for developing countries where limited surveillance and rampant misuse of antimicrobial agents facilitate AMR [6–8]. The World Health Organization (WHO) launched the Global Antimicrobial Resistance Surveillance System (GLASS) in 2015 to standardise AMR surveillance and to evaluate the effect of interventions on AMR in bacterial pathogens [9]. As of February 2020, 98 countries were enrolled in GLASS, including Lebanon, Jordan and Iraq [10].

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Among antimicrobial-resistant pathogens, Gram-negative bacteria (GNB) such as *Acinetobacter* spp., Enterobacteriaceae (i.e. *Escherichia coli*, *Klebsiella* spp. and others) and *Pseudomonas aeruginosa* pose a particular problem and are considered priority pathogens according to the WHO [2,5,11,12]. GNB can acquire resistance to different classes of antimicrobials and can, generally, be classified as multidrug-resistant (MDR; resistant to ≥ 1 antimicrobial agent in ≥ 3 classes), extensively drug-resistant (XDR; resistant to ≥ 1 antimicrobial agent in all but ≤ 2 antimicrobial categories) and pandrug-resistant (PDR; resistant to all antimicrobials) [13]. However, this is a crude subdivision based on phenotypic features, and the exact terminology used to describe GNB is often inconsistent across studies [13].

Typical resistance mechanisms employed by GNB include genetic modifications that increase the expression of antimicrobial-inactivating enzymes or restrict antimicrobial access to the cell (i.e. influx/efflux or permeability alterations) or the introduction of specific AMR genes [3,12,14]. Enzymatic mechanisms of resistance to β -lactams among GNB are largely related to the production of β -lactamases, including extended-spectrum β -lactamases (ESBLs) that hydrolyse multiple antimicrobials including penicillins and cephalosporins. Over 300 different ESBL enzymes harboured in GNB have been identified, but the most common are in the TEM, SHV and CTX-M families [3,12,15]. In addition, overexpression of AmpC β -lactamase can also lead to acquired resistance both to carbapenems and third-generation cephalosporins [3,12]. Although ESBL-producing GNB can be treated with carbapenems, some bacteria now produce β -lactamase carbapenemase enzymes to resist this class of antimicrobial, rendering few therapeutic options for treatment [3]. Among these enzymes, the most notable include KPC, NDM, OXA family, VIM and IMP [12]. For non-enzymatic mechanisms, GNB have also devised means to affect outer membrane permeability to antimicrobials, such as mutations in the *oprD* porin gene that affects carbapenem permeability [3,12,14].

Characterising the epidemiology of these pathogens is a major pillar of the system needed to combat the pervasive threat of MDR bacteria [16]. Furthermore, a better understanding of the mechanisms these pathogens use to evade destruction is critical when treating patients with antimicrobial-resistant infections [16].

Data on clinically prevalent MDR-GNB are particularly limited in low- and middle-income countries [6,7]. This review aimed to evaluate the currently available evidence regarding cephalosporin-, carbapenem- and colistin-resistant GNB infections in Lebanon, Jordan and Iraq from hospital laboratory data focusing on pathogen prevalence, focusing on three main pathogens, namely *Acinetobacter* spp., Enterobacteriaceae (i.e. *E. coli* and *Klebsiella* spp.) and *P. aeruginosa*, as well as the prevalence of phenotypic resistance, genotypic profile and associated mechanisms of resistance.

2. Methods

A literature search of PubMed was performed using the search terms ((Jordan OR Lebanon OR Iraq) AND (Hospital OR patient) AND (Gram negative OR gram-negative OR *Pseudomonas aeruginosa* OR Enterobacter* OR *Acinetobacter baumannii* OR *Escherichia coli* OR *Klebsiella pneumoniae*) AND (resistance*) AND (multidrug OR multi-drug OR cephalosporins OR ESBL OR AmpC OR carbapenem OR colistin OR beta lactam* OR betalactam* OR betalactam*)). The literature search was limited to articles published from 1 January 2015 to 19 August 2020; no language restrictions were applied. Publications were reviewed to identify those articles reporting on AMR profiles and associated mechanisms underlying resistance of GNB among patients in Lebanon, Iraq and Jordan. Articles were excluded if they did not report original research at the phenotypic or molecular level (i.e. reviews, editorials, modelling studies and opinions) or reported data on non-human spec-

imens, specimens collected outside of the three abovementioned countries, or on a single specimen/isolate.

3. Results

Of 153 unique articles retrieved from the PubMed database search, 67 articles met the inclusion criteria, including 40 articles describing studies in Lebanon (including 2 articles reporting studies both in Lebanon and Jordan), 15 articles describing studies in Jordan and 12 articles describing studies conducted in Iraq (Fig. 1).

3.1. Studies in Lebanon

A total of 40 studies investigating AMR in GNB in Lebanon were reviewed: 11 studies in *Acinetobacter* spp. (predominantly identified as *Acinetobacter baumannii*) [17–27], 14 studies in Enterobacteriaceae [28–41], 3 studies in *P. aeruginosa* [42–44], 6 syndrome- or treatment-based studies evaluating multiple GNB [45–50] and 6 hospital surveys also investigating a range of GNB [51–56] (Table 1). Two of the included studies were set across hospitals located in Lebanon and Jordan [34,47].

3.1.1. Resistance of *Acinetobacter baumannii*

Of the studies evaluating *Acinetobacter* spp. isolates that reported phenotypic antimicrobial testing results, all found a high prevalence of carbapenem resistance [17–22,24–27]. The lowest prevalence of carbapenem-resistant *A. baumannii* (CRAB) (55%) was observed during the earliest time period reported (2007–2008); however, when an extended time within the same hospital was considered (2007–2014), the prevalence increased to 74% [22]. In the other studies, carbapenem resistance ranged from 60% [26] to 100% [25,27], with the majority reporting resistance rates $\geq 88\%$ [18,19,21,24,27]. One of the included studies, which was set in multiple medical institutes in Tripoli from 2011–2013, identified a significantly higher rate of CRAB in isolates obtained from Syrian refugee patients compared with Lebanese patients (74% vs. 47%; $P < 0.01$) [26]. Overall, colistin resistance rates in *A. baumannii* remained low, with reported susceptibilities of 99–100% [18–20,22,24,25,27].

Results from the eight studies that were carried out on the genotypic characterisation of β -lactamase genes in CRAB [17,19–21,23,24,26,27] revealed a high frequency of the *bla*_{OXA-23}-like gene and, when typing of isolates was also performed, the predominance of international clone II was apparent [17,19,20,24,26,27]. Furthermore, a study that analysed CRAB isolates from patients treated in the intensive care unit (ICU) of a single hospital observed that the prevalence of *bla*_{OXA-23} increased from 77% during a 2007–2008 outbreak to 95% during an outbreak in 2013 [23]. The second most identified carbapenemase gene type was *bla*_{OXA-24/40-like} [17,19–21,23,24,27], albeit at a considerably lower rate than *bla*_{OXA-23} in all but one study [24]. The single study identified two distinct clones during an outbreak of CRAB in one hospital: one clone was pMAL-1-linked and harboured the OXA-24 variant *bla*_{OXA-72}, and the other was Tn2006-linked and contained *bla*_{OXA-23}; each clone accounted for 19 of the 41 isolates collected [24]. A high prevalence of the carbapenemase gene *bla*_{GES-11} was observed in a study that analysed CRAB isolates collected from patients in multiple hospitals located in the northern part of the country [21]. Of the 142 isolates characterised, 139 (98%) harboured *bla*_{OXA-23}, most of which co-harboured *bla*_{GES-11} (128/139). PCR fingerprinting analyses identified 18 different clones, with 1 clone predominating in several hospitals, suggesting that horizontal spread by clonal diffusion of resistance genes had occurred [21]. Only two studies detected the metallo- β -lactamase (MBL) gene *bla*_{NDM-1}, both finding it at a low prevalence in CRAB isolates (4.4% and 7.1%) [17,26].

Table 1

Studies of antimicrobial resistance (AMR) rates and mechanisms in Gram-negative bacteria (GNB) from Lebanon

Article	Study period	Study population	Pathogens reviewed	Observations related to AMR	Observations related to mechanisms of resistance
Studies investigating <i>Acinetobacter</i> spp./ <i>Acinetobacter baumannii</i> Al Atrouni et al., 2016 [17]	Oct. 2013 to Dec. 2015	Patients (all ages) treated at 7 hospitals in North Lebanon, Beirut and Mount Lebanon	119 non-replicate <i>A. baumannii</i> isolates	91/119 isolates (76%) were resistant to carbapenems	<u>Carbapenemase genes were detected in all 91 carbapenem-resistant isolates:</u> <ul style="list-style-type: none"> • 76 isolates carried <i>bla</i>_{OXA-23-like} only • 3 isolates carried <i>bla</i>_{OXA-24-like} only • 4 isolates carried <i>bla</i>_{NDM-1} only • 1 isolate carried <i>bla</i>_{OXA-143-like} only • 6 isolates carried both <i>bla</i>_{OXA-23-like} and <i>bla</i>_{OXA-24-like} • 1 isolate carried both <i>bla</i>_{OXA-23-like} and <i>bla</i>_{OXA-58-like} • <i>bla</i>_{IMP} and <i>bla</i>_{VIM} were not detected MLST of all 119 isolates revealed 30 STs, with ST2 most common (73/119) PFGE of all ST2 isolates showed a major cluster of 52 carbapenem-resistant isolates (which all harboured <i>bla</i> _{OXA-23-like}) and 1 carbapenem-susceptible isolate, indicating dissemination of IC II NR
Ballouz et al., 2017 [18]	Jun. 2010 to Mar. 2015	Patients (all ages) admitted to a single hospital in Beirut who developed <i>A. baumannii</i> bacteraemia	<i>A. baumannii</i>	<u>Of 90 <i>A. baumannii</i> bacteraemia episodes:</u> <ul style="list-style-type: none"> • 82/90 (91%) were carbapenem-resistant • 79/90 (88%) were deemed XDR Isolates were highly resistant to, ceftazidime and cefepime (both >90%) and most were susceptible to colistin (100%)	
Dahdouh et al., 2016 [19]	Jun. 2013 to Aug. 2014	Clinical isolates from hospitalised patients (all ages) treated at a university medical centre	<i>Acinetobacter</i> spp.: <ul style="list-style-type: none"> • <i>A. baumannii</i>, <i>n</i> = 90 • <i>A. haemolyticus</i>, <i>n</i> = 3 • <i>A. junii/johnsonii</i>, <i>n</i> = 1 • <i>A. radioresistens/lwoffii</i>, <i>n</i> = 1 	<u><i>A. baumannii</i> isolates:</u> <ul style="list-style-type: none"> • 81/90 (90%) were resistant to meropenem and imipenem • 1 isolate was resistant to colistin • Susceptibility to other tested antimicrobials was ≤14% (i.e. cefotaxime, ceftazidime, cefepime) <u>Of the 100 <i>Acinetobacter</i> spp. isolates, resistance rates were:</u> <ul style="list-style-type: none"> • 95% to cefoxitin (all of the <i>A. baumannii</i> isolates) • 81–83% to cefotaxime and ceftazidime • 84% to meropenem and 78% to imipenem • 61% to cefepime • 19% of isolates showed resistance to colistin by disk diffusion, but only 1 isolate showed resistance by microdilution Phenotypically, ESBL production was detected in 23% of the isolates, KPC in 15%, AmpC overproduction in 5% and MBL in 4%	<u>Of the 81 carbapenem-resistant <i>A. baumannii</i> isolates:</u> <ul style="list-style-type: none"> • <i>bla</i>_{OXA-23-like}: <i>n</i> = 74 (91%), with 2/74 additionally harbouring <i>bla</i>_{OXA-24-like} • <i>bla</i>_{OXA-58-like}, <i>bla</i>_{OXA-48}, <i>bla</i>_{NDM} and <i>bla</i>_{KPC} were not detected Trilocus PCR typing determined that 80/90 <i>A. baumannii</i> isolates pertained to IC II; this clone was associated with carbapenem resistance and <i>bla</i> _{OXA-23-like} (<i>P</i> < 0.01) <u>PCR detection of resistance genes:</u> <ul style="list-style-type: none"> • <i>bla</i>_{ADC} in 93% • <i>bla</i>_{OXA-23-like} in 77% • <i>bla</i>_{OXA-24/40-like} in 3% • Two isolates harboured both <i>bla</i>_{OXA-23-like} and <i>bla</i>_{OXA-24/40-like} • <i>bla</i>_{VIM}, <i>bla</i>_{IMP}, <i>bla</i>_{NDM}, <i>bla</i>_{GES}, <i>bla</i>_{OXA-48} and <i>bla</i>_{OXA-58-like} and plasmid-mediated <i>bla</i>_{AmpC} genes were not detected Trilocus PCR typing showed that IC II predominated (82/95 isolates)
Hajjar Soudeihia et al., 2018 [20]	Jun. 2013 to Jun. 2014	Patients (age not stated) admitted to a single hospital	<i>Acinetobacter</i> spp.: <ul style="list-style-type: none"> • Of 100 clinical isolates of <i>Acinetobacter</i> spp., 95 were <i>A. baumannii-calcoaceticus</i> (confirmed as <i>A. baumannii</i>) 	<u>Of the 100 <i>Acinetobacter</i> spp. isolates, resistance rates were:</u> <ul style="list-style-type: none"> • 95% to cefoxitin (all of the <i>A. baumannii</i> isolates) • 81–83% to cefotaxime and ceftazidime • 84% to meropenem and 78% to imipenem • 61% to cefepime • 19% of isolates showed resistance to colistin by disk diffusion, but only 1 isolate showed resistance by microdilution Phenotypically, ESBL production was detected in 23% of the isolates, KPC in 15%, AmpC overproduction in 5% and MBL in 4%	
Hammoudi et al., 2015 [21]	Jan. 2012 to Dec. 2012	Patients (age not stated) from 9 hospitals in geographically distinct areas	Imipenem-resistant <i>A. baumannii</i> : <ul style="list-style-type: none"> • During the study period, 638/723 (88%) <i>A. baumannii</i> isolates were imipenem-resistant; 142 of these isolates were analysed 	<u>Of the 142 non-duplicate imipenem-resistant isolates analysed:</u> <ul style="list-style-type: none"> • All showed high resistance to β-lactams • 68 had phenotypic evidence of ADC hyperproduction • 61 had phenotypic evidence of a class A ESBL with carbapenemase • MBL was not detected phenotypically in any isolate 	Majority of isolates (128/142; 90%) showed GES-type carbapenemase (GES-11) concomitant with OXA-23 enzyme; the remaining isolates had either OXA-23 alone, OXA-24 with GES-11, OXA-24 alone, or GES-11 alone All isolates had <i>ISAbal</i> regardless of carbapenem-hydrolysing enzyme; mapping of <i>ISAbal</i> to <i>bla</i> _{ADC} showed that it was adjacent and upstream to <i>bla</i> _{ADC} in 97% of isolates; mapping of <i>ISAbal</i> in <i>bla</i> _{OXA-23} isolates showed that it lay in an immediately adjacent upstream position to <i>bla</i> _{OXA-23} in all Genetic fingerprinting analyses identified 18 different pulsotypes; the variability in pulsotypes suggested horizontal transmission of resistance genes, although a predominant pulsotype present in several hospitals suggested that clonal diffusion had also taken place

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Table 1 (continued)

Article	Study period	Study population	Pathogens reviewed	Observations related to AMR	Observations related to mechanisms of resistance
Kanafani et al., 2018 [22]	2007–2008 (case-control study) 2007–2014 (prospective study)	Patients admitted to the ICU of a single hospital (mean age 61.7 years in case patients and 60.4 years in control patients; mean age 58.3 years in cohort study)	Pathogens reviewed: Case-control study: • 73 cases with <i>Acinetobacter</i> infections from 2007–2008 were included (70/73 were <i>A. baumannii</i>); 84% of infections were hospital-acquired Prospective study: • 128 patients were diagnosed with <i>Acinetobacter</i> infections During an outbreak from 2012–2014, 130 (10%) of 1267 ICU-admitted patients became colonised or infected with MDR <i>A. baumannii</i>	Observations related to AMR: Case-control study: • Majority of <i>Acinetobacter</i> -infected patients (55%) had carbapenem-resistant <i>Acinetobacter</i> ; 26 of these isolates were tested against colistin and found to be susceptible Prospective study: • Of patients with <i>A. baumannii</i> infections, 95 (74%) were carbapenem-resistant (Note: This study defined MDR <i>A. baumannii</i> as an isolate resistant to all tested antimicrobials except colistin and tigecycline) NR	NR
Kanj et al., 2018 [23]	2007–2008; 2013	Patients (age not stated) admitted to the ICU of a single hospital	<i>A. baumannii</i> : • 148 carbapenem-resistant isolates: 93 from an outbreak between 2007–2008; 55 from an outbreak in 2013 (Note: This study is linked with the Kanafani et al. 2018 [22] study described above)	NR	In carbapenem-resistant <i>A. baumannii</i> clinical isolates: <u>2007–2008 outbreak:</u> • 72/93 (77%) of isolates had <i>bla</i> _{OXA-23} -like • 11/68 (16%) had <i>bla</i> _{OXA-24/40} • 19/68 (28%) had <i>bla</i> _{OXA-58} • 15/68 (22%) had <i>bla</i> _{OXA-143} -like <u>2013 outbreak:</u> • 52/55 (95%) had <i>bla</i> _{OXA-23} -like • 2/55 (4%) had <i>bla</i> _{OXA-143} -like No isolate was positive for <i>bla</i> _{OXA-24/40} or <i>bla</i> _{OXA-58} Using RAPD, 31 clusters were identified with a distinct genomic separation between 2007–2008 isolates and 2013 isolates Genetic analysis identified 2 distinct clones, a pMAL-1-linked clone (<i>n</i> = 19 isolates) and a Tn2006-linked clone (<i>n</i> = 19 isolates) that circulated in different hospital wards during an outbreak. • The pMAL-1-linked clone included ST502 and ST2059 isolates harbouring the <i>bla</i> _{OXA-72} gene • The Tn2006-linked clone included ST1305, ST195 and ST218 isolates containing the <i>bla</i> _{OXA-23} gene • The presence of IS <i>Aba1</i> helped facilitate the spread of the Tn2006 transposon across the 3 STs NR
Makke et al., 2020 [24]	Apr. 2016 to Dec. 2016	Hospitalised patients (all ages) at a single hospital	<i>A. baumannii</i> : • 41 isolates collected from 23 patients during a carbapenem-resistant <i>A. baumannii</i> outbreak	Of the 41 <i>A. baumannii</i> isolates characterised, 95% were classified as XDR: • 95% of isolates were resistant to ceftazidime, imipenem and meropenem • 83% were resistant to cefepime • All isolates were susceptible to colistin All XDR <i>A. baumannii</i> isolates were resistant to all antimicrobials except colistin Previous use of carbapenems or piperacillin/tazobactam was 1 of 4 identified independent risk factors for XDR <i>A. baumannii</i> acquisition (OR = 4.20, 95% CI 1.65–11.81; <i>P</i> = 0.002) (Other independent risk factors identified included urinary catheter placement for >6 days, gastrostomy tube and ICU contact pressure for >4 days)	NR
Moghnieh et al., 2016 [25]	Jul. 2012 to Jul. 2013	Patients of all ages (predominantly aged >45 years) who acquired XDR <i>A. baumannii</i> in a hospital ICU	<i>A. baumannii</i> , XDR isolates acquired by 40/257 (16%) ICU patients	All XDR <i>A. baumannii</i> isolates were resistant to all antimicrobials except colistin Previous use of carbapenems or piperacillin/tazobactam was 1 of 4 identified independent risk factors for XDR <i>A. baumannii</i> acquisition (OR = 4.20, 95% CI 1.65–11.81; <i>P</i> = 0.002) (Other independent risk factors identified included urinary catheter placement for >6 days, gastrostomy tube and ICU contact pressure for >4 days)	NR
Nawfal Dagher et al., 2019 [27]	Jan. 2016 to Aug. 2016	<i>A. baumannii</i> isolated from sputum of patients (age not stated) with VAP who were receiving colistin–carbapenem combination therapy	<i>A. baumannii</i> : • 31 isolates	A high rate of MDR was detected across the 31 <i>A. baumannii</i> isolates, including high-level resistance to imipenem in all No isolates were resistant to colistin	29/31 isolates belonged to ST2 and contained the carbapenemase-encoding <i>bla</i> _{OXA-23} gene and the β-lactamase gene <i>bla</i> _{TEM-1} <i>bla</i> _{TEM-1} (<i>bla</i> _{TEM-1}) was identified in all 31 isolates; <i>bla</i> _{OXA-23} -like was identified in 30 (all encoding OXA-23) and <i>bla</i> _{OXA-24} -like in 1 (encoding the OXA-72 variant) <i>bla</i> _{NDM-1} , <i>bla</i> _{OXA-58} , <i>bla</i> _{VIM} , <i>bla</i> _{SHV} , <i>bla</i> _{CTX-M} or <i>mcr-1</i> , -2, -3, -4 and -5 genes were not identified MLST analysis identified 94% of isolates as belonging to ST2 (IC II lineage)

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Table 1 (continued)

Article	Study period	Study population	Pathogens reviewed	Observations related to AMR	Observations related to mechanisms of resistance
Rafei et al., 2015 [26]	2011–2013	Patients (all ages) treated at one of several hospitals in the Tripoli region (59 Syrian refugees and 57 Lebanese)	<i>A. baumannii</i> : • 116 non-duplicate isolates	Of 116 <i>A. baumannii</i> isolates, most were MDR phenotypically and 70 were carbapenem-resistant. Carbapenem-resistant isolates were significantly more prevalent among Syrian refugees than Lebanese patients (74% vs. 47%; $P < 0.01$)	The predominant carbapenem resistance mechanism was presence of the <i>bla</i> _{OXA-23} gene with upstream <i>ISAbal1</i> (65/70 resistant isolates) 5/70 isolates with <i>bla</i> _{NDM-1} were detected. <i>ISAbal1</i> was detected in 101 isolates (including all isolates with <i>bla</i> _{OXA-23}); the <i>ISAbal1/bla</i> _{OXA-51} association was not detected. <i>bla</i> _{OXA-24} , <i>bla</i> _{OXA-58} , <i>bla</i> _{OXA-143} , <i>bla</i> _{IMP} , <i>bla</i> _{VIM} and <i>bla</i> _{KPC} were not detected in any isolate. MLST performed on 57 isolates identified 17 STs, with ST2 (belonging to CC2 and all harbouring <i>ISAbal1/bla</i> _{OXA-23}) predominant (21/57 isolates by MLST and 73/116 isolates predicted based on <i>bla</i> _{OXA-51} variant)
Studies investigating Enterobacteriaceae Studies investigating <i>Escherichia coli</i> and/or <i>Klebsiella</i> spp.					
Christophy et al., 2017 [28]	Feb. 2014 to Jul. 2014	Stool samples from 41 patients (age not stated) with cancer treated at a single hospital in Tripoli	10/41 patients were carrying carbapenem resistant GNB: • <i>E. coli</i> ($n = 5$ isolates)	<i>E. coli</i> isolates showed varying levels of resistance to most of the antimicrobials tested, but not colistin; all were resistant to ertapenem but susceptible or intermediate to imipenem and meropenem	Of the 9 carbapenemase genes screened for, 2 were detected (in <i>E. coli</i> and <i>Enterobacter aerogenes</i>): <i>bla</i> _{VIM} , 1/10 isolates; <i>bla</i> _{OXA-48} , 2/10 isolates). Of the 6 ESBL genes screened for, 3 were detected (all in <i>E. coli</i> isolates): <i>bla</i> _{CTX-M} , 3/10 isolates; <i>bla</i> _{TEM} , 1/10; <i>bla</i> _{OXA} , 1/10
Dagher et al., 2018 [29]	2012–2016	27 carbapenem-resistant <i>E. coli</i> collected from inpatients (age not stated) at a tertiary hospital in Beirut	<i>E. coli</i> , carbapenem-resistant	All isolates were classified as MDR. Prevalence of resistance: • All isolates were resistant to ertapenem, 37% to imipenem and 22% to meropenem	<u>Genes detected by WGS included:</u> • β -lactamases: • <i>bla</i> _{OXA-48} (48%) • <i>bla</i> _{OXA-181} (7%) • <i>bla</i> _{CTX-M-15} (56%) • <i>bla</i> _{CTX-M-24} (19%) • <i>bla</i> _{OXA-1} (52%) • <i>bla</i> _{TEM-1b} (48%) • <i>bla</i> _{OXA-10} (4%) • <i>bla</i> _{TEM-33} (4%) <u>pAmpC cephalosporinases:</u> • <i>bla</i> _{CMY-2} (4%) • <i>bla</i> _{CMY-42} (41%) Of the 12 isolates that were carbapenem-resistant phenotypically but lacked carbapenemase-encoding genes, 9 (75%) showed multiple deletion events and truncations in <i>ompC</i> and <i>ompF</i> porin-encoding genes. PFGE showed high genetic diversity, with the 27 isolates grouped into 21 different pulsotypes; possible clonal dissemination of STs was apparent.
Daoud et al., 2015 [30]	Jan. 2005 to Jan. 2013	All adult inpatients and outpatients with positive urine cultures for GNB at a single hospital	<i>E. coli</i> : • Of 6284 GNB isolates from UTIs documented over an 8-year period, 60–74% each year were <i>E. coli</i>	<u>Regarding <i>E. coli</i> isolates from UTIs:</u> • Over successive years, ESBL production increased (from 12% in 2005 to 25% in 2012) and susceptibility to third- and fourth-generation cephalosporins (86–90% in 2005 and 68–80% in 2012) and aztreonam (85% in 2005 and 68% in 2012) constantly decreased. • Throughout the 8-year study period, susceptibility was highest to imipenem (99–100%) and fosfomycin (99–100%) • ICU <i>E. coli</i> urinary isolates were associated with the lowest rates of susceptibility to most of the antimicrobials tested	<u>Of 88 phenotypically ESBL-producing urinary <i>E. coli</i> isolated in 2012:</u> • 100% had <i>bla</i> _{CTX-M} • 68% had <i>bla</i> _{TEM} • 31% had <i>bla</i> _{SHV} • 30% had <i>bla</i> _{OXA} • 16% harboured 4 different ESBL genes • 13% harboured 3 different ESBL genes • 56% harboured 2 different ESBL genes • 15% harboured only 1 ESBL gene (<i>bla</i> _{CTX-M}) <u>Of 5 carbapenem-resistant <i>E. coli</i> isolates (2 urinary and 3 other):</u> • 2/5 were <i>bla</i> _{CTX-M} , <i>bla</i> _{TEM} , <i>bla</i> _{OXA-48} • 1 was <i>bla</i> _{CTX-M} , <i>bla</i> _{TEM} , <i>bla</i> _{NDM-1} • 1 was <i>bla</i> _{CTX-M} , <i>bla</i> _{SHV} , <i>bla</i> _{OXA-48} • 1 was <i>bla</i> _{OXA-48} only <i>bla</i> _{IMP} , <i>bla</i> _{VIM} , <i>bla</i> _{SIM} , <i>bla</i> _{SPM} and <i>bla</i> _{KPC} were not detected

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Table 1 (continued)

Article	Study period	Study population	Pathogens reviewed	Observations related to AMR	Observations related to mechanisms of resistance
Daoud et al., 2017 [31]	May 2011 to Dec. 2012	Inpatients (age not stated) at 3 major hospitals	300 ESBL-producing <i>E. coli</i> isolates 91 ESBL-producing <i>Klebsiella</i> spp. isolates	All 391 isolates were confirmed ESBL-producers <i>E. coli</i> and <i>Klebsiella</i> spp. isolates exhibited stable susceptibility to third- and fourth-generation cephalosporins and ceftazidime over time Use of ceftazidime and ceftazidime was positively correlated with β -lactam resistance in <i>E. coli</i> Use of ceftazidime and cefuroxime was correlated with antimicrobial resistance in <i>Klebsiella</i> spp.	Across the 3 hospitals: • <i>bla</i> _{CTX-M-15} was the predominant ESBL gene, being detected in 100% of <i>E. coli</i> and 86–100% of <i>Klebsiella</i> spp. isolates • <i>bla</i> _{TEM} was detected in 58–100% of <i>E. coli</i> and 85–90% of <i>Klebsiella</i> spp. • <i>bla</i> _{SHV-5a} was detected in 29–41% of <i>E. coli</i> and 75–100% of <i>Klebsiella</i> spp. <i>bla</i> _{OXA} was detected in 20–47% of <i>E. coli</i> and 23–53% of <i>Klebsiella</i> spp. • 14–31% of <i>E. coli</i> and 18–43% of <i>Klebsiella</i> spp. possessed all 4 of the screened ESBL genes
Ghaddar et al., 2020 [32]	Mar. 2016 to Mar. 2017	Pregnant women (35–37 weeks of gestation) swabbed during routine antenatal visits to clinics in the Beirut area (<i>n</i> = 308; 1 vaginal swab per patient)	ESBL-producing GNB were obtained from 59/308 swabs: • <i>E. coli</i> , <i>n</i> = 43; 73% • <i>Klebsiella pneumoniae</i> , <i>n</i> = 15; 25%	Of the ESBL-producing isolates: • 25% were MDR • All were resistant to ceftazidime and cefotaxime • Most were susceptible to carbapenems (93%); susceptibilities to other antimicrobials included 36% to cefepime	PCR was performed on all 43 <i>E. coli</i> isolates: • <i>bla</i> _{CTX-M} was the most common β -lactamase gene (91%), followed by <i>bla</i> _{TEM} (88%) and <i>bla</i> _{SHV} (44.2%) 38 (88%) isolates carried >1 β -lactamase gene: • Coexistence of <i>bla</i> _{CTX-M} and <i>bla</i> _{TEM} was detected in 19 isolates (44%), <i>bla</i> _{CTX-M} and <i>bla</i> _{SHV} in 3 (7%), and <i>bla</i> _{CTX-M} , <i>bla</i> _{SHV} and <i>bla</i> _{TEM} in 16 (37%) PFGE analysis of 34 <i>E. coli</i> isolates showed 22 distinct clusters with >85% similarity, with cluster 4 prominent in 8 (24%) isolates Molecular characterisation of 307 ESBL-producing isolates: Many isolates produced multiple β -lactamases (i.e. 2 to 4 β -lactamases) 3 major groups of broad-spectrum β -lactamases were detected: <u>ESBLs</u> (<i>bla</i> _{CTX-M-15} most prevalent; several other CTX-M-, SHV- and TEM-types also detected) <u>Class C cephalosporinases (AmpC)</u> <u>Carbapenemases</u> (<i>bla</i> _{OXA-48} most prevalent; <i>bla</i> _{OXA-181} and <i>bla</i> _{OXA-244} also detected) In addition to the 18 strains with OXA-type carbapenemases, 8 NDM-type strains were detected (all in Jordan) The overall prevalence of carbapenemases in the study was 2% Overall, in Jordan compared with Lebanon, there was a higher rate of strains with resistance (<i>P</i> = 0.0005) and a higher rate of CTX-M-type strains (<i>P</i> = 0.0005); no significant differences in prevalence of SHV-, TEM- or OXA-type strains between countries were observed
Hajj et al., 2018 [34] (Lebanon and Jordan)	2011–2015	Patients (age not stated) with IAIs and UTIs from 3 hospitals and 1 laboratory	1486 Enterobacteriaceae pathogens isolated: 651 from IAIs and 835 from UTIs Predominant pathogens: (UTI%/IAI%) • <i>E. coli</i> : 77%/60% • <i>K. pneumoniae</i> : 14%/17%	There was general stability in AMR rates among Enterobacteriaceae during the 5-year study period <u>In <i>E. coli</i> isolates:</u> • ESBL prevalence, UTI/IAI: • Lebanon: 39%/33% • Jordan: 53%/58% • ESBL rates for <i>E. coli</i> in UTIs and IAIs were significantly higher in Jordan compared with Lebanon (<i>P</i> < 0.0001 and <i>P</i> = 0.0003, respectively) • In general, <i>E. coli</i> isolates had high susceptibility to carbapenems, with no significant differences between ESBL and non-ESBL groups <u>In <i>K. pneumoniae</i> isolates:</u> • ESBL prevalence, UTI/IAI: • Lebanon: 38%/64% • Jordan: 59%/54% • ESBL rates for <i>K. pneumoniae</i> in UTIs were significantly higher in Jordan compared with Lebanon (<i>P</i> = 0.0397) • ESBL <i>K. pneumoniae</i> from UTIs in Jordan had significantly lower susceptibility to carbapenems compared with non-ESBL (100% vs. 93%; <i>P</i> < 0.02); Compared with Lebanon, ESBL <i>K. pneumoniae</i> from UTIs in Jordan had lower susceptibility rates for several antimicrobials	
Halimeh et al., 2020 [33]	Jul. 2010 to Sep. 2016	Clinical stool samples from North Lebanon	43 <i>E. coli</i> isolates	21–30% of isolates were resistant to second- and third-generation cephalosporins and 19% to aztreonam No isolates were resistant to carbapenems or colistin 19/43 isolates were phenotypic ESBL-producers, 16 of which were MDR	13/19 phenotypic ESBL-producing isolates were ESBL-positive by PCR: • <i>bla</i> _{CTX-M-1} group detected in 10 isolates • <i>bla</i> _{TEM} group detected in 8 isolates (all <i>bla</i> _{TEM-1}) • <i>bla</i> _{SHV} and <i>bla</i> _{CTX-M-9} not detected

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Table 1 (continued)

Article	Study period	Study population	Pathogens reviewed	Observations related to AMR	Observations related to mechanisms of resistance
Hanna-Wakim et al., 2015 [35]	Jan. 2001 to Dec. 2011	Children and adolescents (age <18 years) hospitalised with UTIs in 2 major hospitals	Of 675 UTI cases included in the analysis, the most prevalent uropathogens included: <ul style="list-style-type: none"> • <i>E. coli</i> (79%) • <i>Klebsiella</i> spp. (8%) • <i>Pseudomonas aeruginosa</i> (2%) 	Of 584 cases caused by <i>E. coli</i> or <i>Klebsiella</i> spp., 91 were ESBL-producing (16%) and 493 were non-ESBL-producing (84%): <ul style="list-style-type: none"> • <i>Klebsiella</i> spp. were more common in the ESBL group compared with the non-ESBL group (18% vs. 8%; $P = 0.02$) • Longer hospital stay was associated with ESBL organisms ($P < 0.001$) • Over the 10-year period, ESBL paediatric UTIs increased from 8% (2001) to 25% (2011); there was a strong linear correlation, with a 2.1% yearly increase • There was also a linear trend of increasing resistance to cephalosporins over the study period, with a 1.2% annual increase 	NR
Kanafani et al., 2017 [37]	Jul. 2011 to Feb. 2014	Adult inpatients ($n = 100$) in a single hospital diagnosed with an infection (urinary, respiratory, blood or skin/soft tissue) due to ESBL-producing <i>E. coli</i> or <i>Klebsiella</i> spp.	ESBL-producing <i>E. coli</i> , (87%) ESBL-producing <i>Klebsiella</i> spp. (13%)	Isolates showed high susceptibility to carbapenems (99%) and low susceptibility to cefepime (<30%)	22 patients had positive cultures at sites additional to the original infection site (i.e. colonisation); isolates from these patients were screened by PCR ($n = 54$ isolates in total): <ul style="list-style-type: none"> • $bla_{CTX-M-15}$ was detected in 80% of isolates and bla_{TEM-1} in 39% • In 11 patients the same <i>bla</i> genes were detected in isolates from different sites • In 10 patients there was minor variation in the <i>bla</i> genes detected in isolates from different sites • PFGE analysis showed that in 11 patients the isolates collected from different sites were genetically identical, whereas in the other patients the isolates from different sites were genetically variable (43–97% similar); several of these patients were colonised with multiple varying strains
Mognieh et al., 2015 [38]	Oct. 2009 to Jan. 2012	Adult cancer chemotherapy patients with fever, neutropenia and positive blood culture admitted to a single hospital (75 bacteraemia episodes in 70 patients)	GNB from bacteraemia (57% of 75 episodes), most frequently: <ul style="list-style-type: none"> • <i>E. coli</i>, 17 isolates: 23% of total; 40% of GNB • <i>K. pneumoniae</i>, 10 isolates: 13% of total; 23% of GNB 	Of all bacteraemia episodes: <ul style="list-style-type: none"> • 29% caused by third-generation cephalosporin-resistant GNB (including 8 <i>E. coli</i> and 5 <i>K. pneumoniae</i> isolates) • 9% caused by carbapenem-resistant GNB 	NR
Nawfal Dagher et al., 2020 [39]	Oct. 2016 to Feb. 2017	Patients (age not stated); hospitalised in an ICU who had received colistin–carbapenem for >1 week (1 rectal swab collected per patient, $n = 23$)	Enterobacteriaceae, colistin-resistant: <ul style="list-style-type: none"> • A total of 12 isolates from 11 patients, including <i>E. coli</i> ($n = 5$) and <i>K. pneumoniae</i> ($n = 1$) 	Of the 8 isolates included in the study: <ul style="list-style-type: none"> • All were resistant to cefalotin and colistin • All were susceptible to ertapenem and imipenem • 6/8 isolates were resistant to the third-generation cephalosporins tested, including all <i>E. coli</i> and <i>K. pneumoniae</i> 	ESBL genes were identified in all 8 isolates: <ul style="list-style-type: none"> • bla_{TEM} in 6/8 (TEM-1 or TEM-163) • bla_{CTX-M} in 4/8 (CTX-M-15, CTX-M-189, CTX-M-15 or CTX-M-103) • bla_{SHV-1} in 1/6 ($bla_{TEM-163}$, $bla_{CTX-M-103}$, $bla_{CTX-M-189}$ and bla_{SHV-1} had not been reported in Lebanon previously) Colistin resistance among the <i>E. coli</i> and <i>K. pneumoniae</i> isolates was due to a variety of missense and deletion mutations, including within <i>pmrA/B</i> , <i>phoP/Q</i> and <i>mgtB</i> genes

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Table 1 (continued)

Article	Study period	Study population	Pathogens reviewed	Observations related to AMR	Observations related to mechanisms of resistance
Nawfal Dagher et al., 2019 [40]	Nov. 2017	5 patients (age not stated) admitted to a single hospital	<i>K. pneumoniae</i> , MDR ($n = 5$ isolates from various clinical specimens)	<u>Of 32 antimicrobials tested:</u> <ul style="list-style-type: none"> All 5 isolates showed high resistance to the main antimicrobials tested 5/5 were resistant to imipenem 2/5 were resistant to colistin 	<u>Carbapenemase genes:</u> <ul style="list-style-type: none"> All 5 isolates harboured <i>bla</i>_{OXA-48} and <i>bla</i>_{NDM-5} genes <i>bla</i>_{OXA-23}, <i>bla</i>_{OXA-24}, <i>bla</i>_{OXA-58} and <i>bla</i>_{KPC} genes were not detected in any isolate <u>Colistin resistance genes:</u> <ul style="list-style-type: none"> None of the strains contained the plasmid-mediated <i>mcr</i> genes Sequence analysis of the 2 colistin-resistant isolates showed that the colistin-resistant phenotypes observed were due to mutation of <i>mgrB</i>, <i>pmrB</i> and <i>phoQ</i> genes <u>MLST analysis:</u> <ul style="list-style-type: none"> All isolates were ST383 <u>ESBL genes:</u> <ul style="list-style-type: none"> 2 isolates harboured <i>bla</i>_{CTX-M-15}, <i>bla</i>_{TEM-12} and <i>bla</i>_{SHV-5} 1 isolate harboured <i>bla</i>_{SHV-5} only <u>Colistin resistance:</u> <ul style="list-style-type: none"> Facilitated by mutations in the <i>mgrB</i>, <i>phoQ</i> and/or <i>pmrB</i> genes; a novel missense mutation in <i>pmrA</i> was also detected in 1 isolate The 3 isolates were of 3 different STs (ST268, ST34 and ST2269), indicating that they were not related
Okdah et al., 2017 [41]	Sep. 2015 to Oct. 2015	Adult patients admitted to a single hospital	<i>K. pneumoniae</i> , colistin resistant ($n = 3$; first reported colistin-resistant isolates in Lebanon)	All 3 isolates were colistin-resistant and resistant to ≥ 5 of the other 15 antimicrobials tested	<u>ESBL genes:</u> <ul style="list-style-type: none"> 2 isolates harboured <i>bla</i>_{CTX-M-15}, <i>bla</i>_{TEM-12} and <i>bla</i>_{SHV-5} 1 isolate harboured <i>bla</i>_{SHV-5} only <u>Colistin resistance:</u> <ul style="list-style-type: none"> Facilitated by mutations in the <i>mgrB</i>, <i>phoQ</i> and/or <i>pmrB</i> genes; a novel missense mutation in <i>pmrA</i> was also detected in 1 isolate The 3 isolates were of 3 different STs (ST268, ST34 and ST2269), indicating that they were not related
Studies investigating other Enterobacteriaceae Kanafani et al., 2016 [36]	2011–2014	Patients (age not stated) with CRE infections at a single hospital ($n = 40$)	Enterobacteriaceae, carbapenem-resistant	Between 2011–2013 at the hospital, CRE incidence increased >70% of CRE isolates were susceptible to colistin	NR
Studies investigating <i>Pseudomonas aeruginosa</i> El Kary et al., 2016 [42]	Jan. 2013 to Jul. 2013	Inpatients diagnosed with <i>P. aeruginosa</i> infection at a single hospital (mean age, 61 years; $n = 135$)	<i>P. aeruginosa</i> <ul style="list-style-type: none"> RTIs, 40%; UTIs, 26%; cutaneous infections, 22%; blood, 4% 	<u>Resistance rates were:</u> <ul style="list-style-type: none"> Imipenem, 19% Both Imipenem and ciprofloxacin, 29% Imipenem resistance significantly more frequent in patients receiving carbapenem or other antimicrobials or hospitalisation within the previous 3 months Combined resistance significantly more frequent in patients receiving carbapenem or hospitalisation in the previous 3 months The 4 <i>P. aeruginosa</i> isolates were resistant to all antimicrobials tested except colistin and fosfomycin All 4 isolates were carbapenemase-positive by phenotypic test	NR
Nawfal Dagher et al., 2019 [43]	Oct. 2016 to Feb. 2017	ICU patients (age not stated) in a single hospital treated with carbapenem for >1 week (rectal swabs collected from 23 patients)	<i>P. aeruginosa</i> , carbapenem-resistant ($n = 4$ isolates)	The 4 <i>P. aeruginosa</i> isolates were resistant to all antimicrobials tested except colistin and fosfomycin All 4 isolates were carbapenemase-positive by phenotypic test	3/4 isolates harboured the MBL gene <i>bla</i> _{VIM-2} All isolates had mutations in the <i>oprD</i> gene 3 isolates were ST357 (i.e. the 3 isolates with <i>bla</i> _{VIM-2}) and 1 isolate was ST233
Yaghi et al., 2020 [44]	Mar. 2015 to Oct. 2015	Patients (age not stated) with hospital-acquired UTIs in a single hospital	<i>P. aeruginosa</i> , MDR ($n = 40$ isolates)	40 isolates of MDR <i>P. aeruginosa</i> were isolated from UTIs during the sample collection time period; 12 of the MDR strains, susceptible only to colistin, were selected for genetic and protein analyses	<u>Of the 12 selected <i>P. aeruginosa</i> strains susceptible only to colistin:</u> <ul style="list-style-type: none"> 75% were positive for <i>bla</i>_{GES-6} 50% and 17% were positive for <i>bla</i>_{VIM-2} and <i>bla</i>_{IMP-15}, respectively Proteomic analyses detected several proteins involved in the MDR phenotype, including co-existence of class C β-lactamases AmpC and PDC-13, motility protein flagellin and several putative virulence proteins Regarding further non-enzymatic mechanisms of resistance, downregulation or mutation of the <i>oprD2</i> gene (encoding a carbapenemase-selective porin) was also implicated

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Article	Study period	Study population	Pathogens reviewed	Observations related to AMR	Observations related to mechanisms of resistance
Syndrome- or treatment-based studies investigating several GNB species Awad et al., 2018 [45]	Jul. 2015 to Jul. 2016	43 patients (age not stated) with 61 VAP episodes in the ICU of a single hospital	72/75 isolates were GNB, including: • <i>A. baumannii</i> , 37%; <i>n</i> = 28 • <i>P. aeruginosa</i> , 31%, <i>n</i> = 23 • Enterobacteriaceae, 15%; <i>n</i> = 11	<i>A. baumannii</i> isolates: • 93% XDR, 4% MDR, 4% PDR (XDR <i>A. baumannii</i> : carbapenem-resistant and susceptible only to polymyxins ± glycolcyclines) <i>P. aeruginosa</i> isolates: • 13% XDR (XDR <i>P. aeruginosa</i> : resistant to all tested available antimicrobials except polymyxins) • 57% susceptible to carbapenems • 74% susceptible to ceftazidime Enterobacteriaceae isolates: • 82% susceptible to cefepime • 73% susceptible to third-generation cephalosporins • 100% susceptible to carbapenems <i>P. aeruginosa</i> : • 45–60% resistant to all carbapenems and cephalosporins tested; lowest resistance against colistin (5%) <i>A. baumannii</i> : • >88% resistant to 11/16 antimicrobials tested, including all carbapenems and cephalosporins; lowest resistance to aztreonam and colistin (all 0%) <i>E. coli</i> : • No resistance to colistin; low resistance to carbapenems (0–7%); moderate resistance to cephalosporins (39–43%) <i>K. pneumoniae</i> : • No resistance to colistin; low resistance to carbapenems (0–14%); moderate resistance to cephalosporins (39–53%)	NR
Bourgi et al., 2020 [46]	Jan. 2014 to Dec. 2018	475 patients (all ages) admitted to a hospital burn care centre	Of 261 patients with infections (wound 58%, blood 30%, sputum 8%, urine 7%, catheter 2%), GNB were isolated in 134, predominantly: • <i>P. aeruginosa</i> (<i>n</i> = 59) • <i>A. baumannii</i> (<i>n</i> = 41) • <i>E. coli</i> (<i>n</i> = 19) • <i>K. pneumoniae</i> (<i>n</i> = 18)	<i>A. baumannii</i> : • 45–60% resistant to all carbapenems and cephalosporins tested; lowest resistance against colistin (5%) <i>A. baumannii</i> : • >88% resistant to 11/16 antimicrobials tested, including all carbapenems and cephalosporins; lowest resistance to aztreonam and colistin (all 0%) <i>E. coli</i> : • No resistance to colistin; low resistance to carbapenems (0–7%); moderate resistance to cephalosporins (39–43%) <i>K. pneumoniae</i> : • No resistance to colistin; low resistance to carbapenems (0–14%); moderate resistance to cephalosporins (39–53%)	NR
Hayajneh et al., 2015 [47] (Lebanon and Jordan)	2011–2013	GNB isolates from UTIs and IAIs were collected from laboratories at participating hospitals (2 in Jordan, 2 in Lebanon); patient age not stated	Of 1050 GNB isolates, 523 were from UTIs and 527 from IAIs: UTIs: • <i>E. coli</i> , 70% • <i>K. pneumoniae</i> , 14% • <i>P. aeruginosa</i> , 3% • <i>A. baumannii</i> , 2% • Others, 5% IAIs: • <i>E. coli</i> , 46% • <i>K. pneumoniae</i> , 14% • <i>P. aeruginosa</i> , 12% • <i>A. baumannii</i> , 5% • Others, 9%	ESBL prevalence was 43% and 54% among UTI <i>E. coli</i> and <i>K. pneumoniae</i> isolates, respectively; corresponding rates for IAI isolates were 49% and 56%, respectively ESBL-producing <i>E. coli</i> isolates remained stably susceptible to carbapenems during the study period, whereas ESBL-producing <i>K. pneumoniae</i> showed decreased susceptibility over time (100% in 2011 to 88% in 2013) Compared with non-ESBL isolates, ESBL-producing <i>E. coli</i> and <i>K. pneumoniae</i> were less susceptible to most of the tested antimicrobials <i>A. baumannii</i> showed low susceptibility rates to the antimicrobials tested (4–27%), being most susceptible to imipenem (27% of isolates from UTIs and 8% of isolates from IAIs)	

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Table 1 (continued)

Article	Study period	Study population	Pathogens reviewed	Observations related to AMR	Observations related to mechanisms of resistance
				<i>P. aeruginosa</i> showed susceptibility rates of 29–89%, with 53% of isolates from UTIs and 75% of isolates from IAls being susceptible to imipenem	In 204 ESBL-producing Enterobacteriaceae isolates: <ul style="list-style-type: none"> • Mostly <i>E. coli</i> ($n = 145$) and <i>K. pneumoniae</i> ($n = 49$) ESBL genes: <ul style="list-style-type: none"> • <i>bla</i>_{CTX-M-15}, $n = 178$ • <i>bla</i>_{CTX-M-14}, $n = 5$ • <i>bla</i>_{CTX-M-27}, $n = 4$ • <i>bla</i>_{CTX-M3}, $n = 2$ • <i>bla</i>_{CTX-M-1}, <i>bla</i>_{CTX-M-55}, <i>bla</i>_{CTX-M-9}, <i>bla</i>_{CTX-M-24}, all $n = 1$ • <i>bla</i>_{SHV-12}, $n = 11$ • <i>bla</i>_{SHV-28}, $n = 6$ • <i>bla</i>_{SHV-5}, $n = 1$ • <i>bla</i>_{TEM-169}, <i>bla</i>_{TEM-33}, <i>bla</i>_{TEM-52}, all $n = 1$ • <i>bla</i>_{VEB-4}, $n = 1$ • Many isolates harboured ≥ 1 ESBL gene Carbapenemase genes: <ul style="list-style-type: none"> • Of the 17 isolates that were non-susceptible to carbapenems, 10 had <i>bla</i>_{OXA-48}, 7 had <i>bla</i>_{NDM-1} and 1 had <i>bla</i>_{KPC-2} AmpC genes: <ul style="list-style-type: none"> • AmpC genes were detected in 15 isolates
Ismail et al., 2016 [48]	Jan. 2007 to Dec. 2011	Patients (aged <21 years) admitted to the paediatric ICU at a single hospital who developed DA-HAls	In 22 patients who developed 59 DA-HAls: <ul style="list-style-type: none"> • <i>Klebsiella</i> spp., 17% • <i>Pseudomonas</i> spp., 12% • <i>E. coli</i>, 10% • <i>Enterobacter</i> spp., 7% • <i>Acinetobacter</i> spp., <i>Stenotrophomonas maltophilia</i>, <i>Serratia marcescens</i>, 7% 	80% of <i>K. pneumoniae</i> isolates and 67% of <i>E. coli</i> isolates were ESBL-producers All <i>Klebsiella</i> spp. isolates were susceptible to imipenem and ceftioxin 29% of <i>Pseudomonas</i> spp. were MDR and 43% were resistant to imipenem Of 6 <i>P. aeruginosa</i> isolates, 2 were MDR (i.e. resistant to β -lactams, carbapenems, aminoglycosides and fluoroquinolones) The single <i>A. baumannii</i> isolate was MDR	NR
Jouhar et al., 2020 [49]	Jan. 2008 to Jun. 2017	Patients (mean age 66.9 \pm 12.2 years; $n = 356$) admitted to a single hospital with DFU	314 isolates were obtained from 179 patients who underwent deep tissue culture 174 isolates (55%) were GNB: <ul style="list-style-type: none"> • Enterobacteriaceae, $n = 132$ (<i>E. coli</i>, $n = 47$) • <i>P. aeruginosa</i>, $n = 34$ • <i>Acinetobacter</i>, $n = 8$ GNB were 304/374 isolates (81%) <ul style="list-style-type: none"> <i>A. baumannii</i>, 105/374 (28%) <i>E. coli</i>, 60/374 (16%) <i>Klebsiella</i> spp., 48/374 (13%) <i>P. aeruginosa</i>, 45/374 (12%) 	Enterobacteriaceae: <ul style="list-style-type: none"> • 25% ESBL-producers • 2% resistant to carbapenems <i>P. aeruginosa</i> : <ul style="list-style-type: none"> • 3% resistant to carbapenems, 8% to cephalosporins <i>Acinetobacter</i> : <ul style="list-style-type: none"> • 37% MDR <i>A. baumannii</i> : <ul style="list-style-type: none"> • 85% (87/102) were resistant to carbapenems <i>E. coli</i> : <ul style="list-style-type: none"> • 77% (46/60) were resistant to third-generation cephalosporins; no carbapenem resistance was detected <i>Klebsiella</i> spp.: <ul style="list-style-type: none"> • Approximately 39% (18/48) of isolates were resistant to third-generation cephalosporins; no carbapenem resistance was detected <i>P. aeruginosa</i> : <ul style="list-style-type: none"> • 44% (20/45) were carbapenem resistant 	NR
Moghnieh et al., 2017 [50]	Jan. 2012 to Dec. 2013	153 adult (predominantly ≥ 65 years) patients at a single hospital who received tigecycline for >72 h	GNB were 304/374 isolates (81%) <ul style="list-style-type: none"> <i>A. baumannii</i>, 105/374 (28%) <i>E. coli</i>, 60/374 (16%) <i>Klebsiella</i> spp., 48/374 (13%) <i>P. aeruginosa</i>, 45/374 (12%) 	<i>A. baumannii</i> : <ul style="list-style-type: none"> • 85% (87/102) were resistant to carbapenems <i>E. coli</i> : <ul style="list-style-type: none"> • 77% (46/60) were resistant to third-generation cephalosporins; no carbapenem resistance was detected <i>Klebsiella</i> spp.: <ul style="list-style-type: none"> • Approximately 39% (18/48) of isolates were resistant to third-generation cephalosporins; no carbapenem resistance was detected <i>P. aeruginosa</i> : <ul style="list-style-type: none"> • 44% (20/45) were carbapenem resistant 	NR

Hospital surveys investigating several GNB species

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Table 1 (continued)

Article	Study period	Study population	Pathogens reviewed	Observations related to AMR	Observations related to mechanisms of resistance
Chamieh et al., 2020 [51]	Jan. 2010 to Jun. 2018	Clinical microbiology isolates from a tertiary care centre in Beirut	2150 carbapenem-resistant GNB isolates including: <ul style="list-style-type: none"> • <i>A. baumannii</i> (42%) • <i>P. aeruginosa</i> (23%) • <i>E. coli</i> (5.7%) • <i>K. pneumoniae</i> (5%) 	Beginning in 2016, a trend of increased imipenem resistance among carbapenem-resistant organisms was observed ($P = 0.098$) Isolation density of carbapenem-resistant <i>E. coli</i> increased steadily from 2012, whereas carbapenem-resistant <i>K. pneumoniae</i> showed a 4-fold increase in 2018 following a clonal outbreak of ST383 <i>K. pneumoniae</i> (carbapenem- and colistin-resistant) in late 2017 Correspondingly, the percentage of CRE out of all carbapenem-resistant organisms increased from 3% in 2010–2011 to 8% until 2017 before rising sharply to 32% in 2018 Mean ESBL production: <ul style="list-style-type: none"> • <i>E. coli</i>: 32% • <i>K. pneumoniae</i>: 29% 	NR
Chamoun et al., 2016 [52]	Jan. 2011 to Dec. 2013	Bacterial isolates from 16 different tertiary care centres, representing 41% of hospital beds in Lebanon; patient age not stated	55 594 GNB isolates: <ul style="list-style-type: none"> • <i>E. coli</i> (55%) • <i>P. aeruginosa</i> (14%) • <i>Klebsiella</i> spp. (14%) • <i>Acinetobacter</i> spp. (6%) • <i>Enterobacter</i> spp. (4%) • Others (7%) 	Antimicrobial susceptibilities: <ul style="list-style-type: none"> • <i>E. coli</i>: most susceptible to imipenem (mean resistance, 0.7%); susceptibility to most cephalosporins showed a statistically significant decreasing trend • <i>K. pneumoniae</i>: most susceptible to imipenem (98%) • <i>Acinetobacter</i> spp.: decreased imipenem susceptibility rate from 2011 to 2013 (49% to 15%); high susceptibility to colistin (96% in 2013) • <i>Pseudomonas</i> spp.: mean of 73% susceptible to imipenem (decreasing susceptibility from 80% in 2011 to 73% in 2013) 	NR
Hammoudi et al., 2015 [53]	Jan. 2011 to Jun. 2011; Jan. 2012 to Jun. 2012	Carbapenem-non-susceptible GNB isolates collected from patients (all ages) at a single hospital	In 2011: <ul style="list-style-type: none"> • 197/821 GNB isolates were carbapenem-non-susceptible Of 48 isolates analysed: <ul style="list-style-type: none"> • <i>K. pneumoniae</i>, $n = 1$ • <i>A. baumannii</i>, $n = 4$ • <i>P. aeruginosa</i>, $n = 40$ • <i>Pseudomonas</i> spp., $n = 3$ In 2012: <ul style="list-style-type: none"> • 267/930 GNB isolates were carbapenem-non-susceptible Of 100 isolates analysed: <ul style="list-style-type: none"> • <i>K. pneumoniae</i>, $n = 1$ • <i>A. baumannii</i>, $n = 8$ • <i>P. aeruginosa</i>, $n = 75$ • <i>Pseudomonas</i> spp., $n = 12$ 	<i>K. pneumoniae</i> : <ul style="list-style-type: none"> • Both isolates showed possible carbapenemase production phenotypically and 1 isolate was resistant to tested cephalosporins and imipenem <i>P. aeruginosa</i> and <i>Pseudomonas</i> spp.: <ul style="list-style-type: none"> • High resistance to all antimicrobials tested 	<i>K. pneumoniae</i> : <ul style="list-style-type: none"> • 2 isolates were analysed: <ul style="list-style-type: none"> • <i>bla</i>_{OXA-48} and IS1999 were detected in both isolates • An AmpC gene was additionally detected in 1 isolate and <i>bla</i>_{CTX-M-1} in the other <i>A. baumannii</i> : <ul style="list-style-type: none"> • 12 isolates were analysed: <ul style="list-style-type: none"> • <i>bla</i>_{OXA-23} detected in 11/12 • <i>bla</i>_{OXA-24} in 1/12 • <i>bla</i>_{GES-11} in 5/12 (all in conjunction with <i>bla</i>_{OXA-23}) <i>P. aeruginosa</i> : <ul style="list-style-type: none"> • 21 isolates with high-level imipenem resistance were analysed: <ul style="list-style-type: none"> • <i>bla</i>_{VIM-2} detected in 17/21 • <i>bla</i>_{IMP-1} in 2/21 • <i>bla</i>_{IMP-2} in 2/21 <i>Pseudomonas</i> spp.: <ul style="list-style-type: none"> • 3 isolates with high-level imipenem resistance were analysed: <ul style="list-style-type: none"> • <i>bla</i>_{VIM-2} detected in 3/3

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Table 1 (continued)

Article	Study period	Study population	Pathogens reviewed	Observations related to AMR	Observations related to mechanisms of resistance
Hammoudi Halat et al., 2017 [54]	Jan. 2012 to Dec. 2012	Patients (age not stated) at 11 tertiary care centres	Among 12 045 isolates: • Enterobacteriaceae, $n = 9485$ • <i>A. baumannii</i> , $n = 712$ • <i>Pseudomonas</i> (including <i>P. aeruginosa</i> and <i>Pseudomonas</i> spp.), $n = 1848$	Carbapenem non-susceptible rates: • 88% of <i>A. baumannii</i> • 41% of <i>Pseudomonas</i> • 1.2% of Enterobacteriaceae Of the <i>A. baumannii</i> isolates tested, all were resistant to any antimicrobial tested <i>Pseudomonas</i> isolates were resistant to all antimicrobials tested except colistin	Of the 398 isolates studied, 55% had genetically detectable carbapenemase production: Among Enterobacteriaceae ($n = 44$): • 70% of isolates harboured the <i>bla</i> _{OXA-48-like} gene on IncI/M-type plasmids, with 90% of these isolates also carrying IS1999 • Other resistance mechanisms included ESBL production (the majority of isolates had an ESBL of CTX-M-1- or SHV-type in addition to <i>bla</i> _{OXA-48-like} gene) and acquisition of AmpC cephalosporinase, and there was phenotypic evidence of efflux pump expression in some isolates Among <i>A. baumannii</i> ($n = 142$): • Most isolates harboured <i>bla</i> _{OXA-23} (98%) and/or <i>bla</i> _{GES-11} (92%) genes (90% of isolates carried both) • The <i>bla</i> _{OXA-24} gene (1.4%) was also identified, for the first time in Lebanese isolates • IS <i>Aba1</i> was detected in all isolates Among <i>Pseudomonas</i> ($n = 212$): • 21% of <i>P. aeruginosa</i> and 27% of <i>Pseudomonas</i> spp. had either <i>bla</i> _{IMP} or <i>bla</i> _{VIM} MBL genes (MBL production was detected phenotypically in 22% of <i>P. aeruginosa</i> and 27% of <i>Pseudomonas</i> spp.) NR
Matta et al., 2018 [55]	Study duration 6 months (dates not reported)	258 adult patients admitted to 5 different hospitals who had community-acquired infections ($n = 116$) or who developed hospital-acquired infections ($n = 142$)	171/221 isolates were GNB (77%), including: • <i>E. coli</i> • <i>P. aeruginosa</i> • <i>K. pneumoniae</i> • <i>A. baumannii</i> (and other GNB species)	ESBL-producing <i>E. coli</i> occurred at significantly higher frequency in hospital-acquired infections compared with community-acquired infections (30% vs. 13%; $P = 0.001$), whereas no significant difference in frequency of ESBL-producing <i>K. pneumoniae</i> was observed (1.7% vs. 0.7%) MDR <i>Pseudomonas</i> was more frequently observed among hospital-acquired isolates compared with community-acquired isolates (14% vs. 3%; $P = 0.001$)	NR
Mognieh et al., 2019 [56]	2015–2016	Antimicrobial susceptibility data from 13 hospital laboratories (different patient populations; e.g. paediatric, adult, critically ill, pregnant, outpatients)	Of 85 144 clinical isolates 76% were GNB, including: • <i>E. coli</i> • <i>Klebsiella</i> spp. • <i>P. aeruginosa</i> • <i>Acinetobacter</i> spp.	<u>Enterobacteriaceae:</u> • <i>E. coli</i> and <i>Klebsiella</i> spp. combined were 59% susceptible to third-generation cephalosporins and 97% susceptible to carbapenems; ESBL production was observed in 34% <u><i>P. aeruginosa</i>:</u> • Susceptibility to carbapenems ranged from 55–95% across all hospitals; 98% colistin-susceptible <u><i>Acinetobacter</i> spp.:</u> • From 11 hospitals, 12% of isolates were susceptible to carbapenems (range, 3–74%) Compared with 2011–2013 surveillance data [52], decreased antimicrobial susceptibility was observed for priority pathogens: • Carbapenem-resistant <i>Acinetobacter</i> , <i>P. aeruginosa</i> , <i>Klebsiella</i> spp. and <i>E. coli</i> • Third-generation cephalosporin-resistant <i>Klebsiella</i> spp. and <i>E. coli</i>	NR

CC, clonal complex; CI, confidence interval; CRE, carbapenem-resistant Enterobacteriaceae; DA-HAI, device-associated healthcare-associated infection; DFU, diabetic foot ulcer; ESBL, extended-spectrum β -lactamase; IAI, intra-abdominal infection; IC, international clone; ICU, intensive care unit; IS, insertion sequence; MBL, metallo- β -lactamase; MDR, multidrug-resistant; MLST, multilocus sequence typing; NR, not recorded; OR, odds ratio; pAmpC, plasmid-mediated AmpC; PDR, pandrug-resistant; PFGE, pulsed-field gel electrophoresis; RAPD, random amplification of polymorphic DNA; RTI, respiratory tract infection; ST, sequence type; UTI, urinary tract infection; VAP, ventilator-associated pneumonia; WGS, whole-genome sequencing; XDR, extensively drug-resistant.

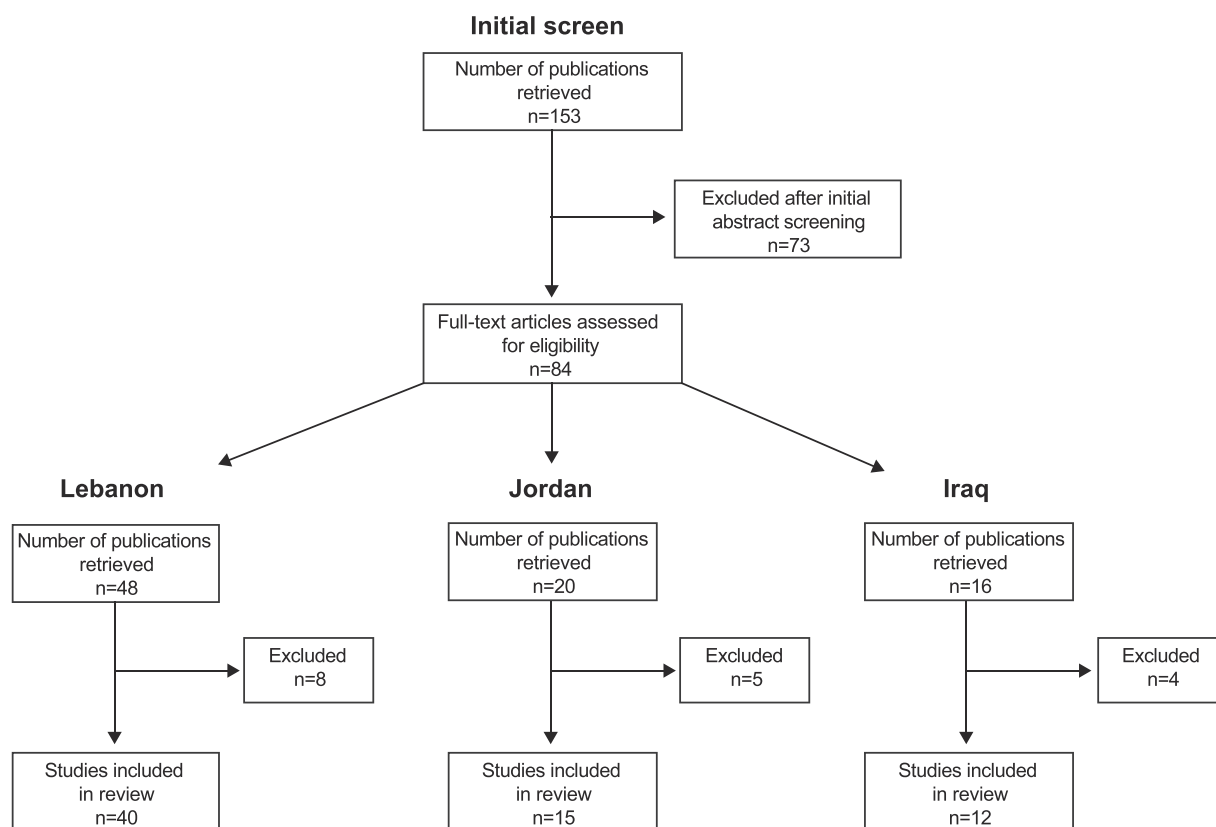


Fig. 1. Flow chart of publications identified and included in the review.

3.1.2. Resistance of Enterobacteriaceae

Fourteen studies investigated AMR in Enterobacteriaceae isolates [28–41]. The reported data indicated that the prevalence of ESBL-producing isolates ranged from 11.6% [in *E. coli* isolated from urinary tract infections (UTIs) sampled during 2005] [30] to 64% [in *Klebsiella pneumoniae* isolated from intra-abdominal infections (IAIs) in Lebanon during 2011–2015] [34]. In the former study, the prevalence of ESBL production in *E. coli* UTI isolates increased over time, from 12% in 2005 to 25% in 2012 [30]. The latter study found the prevalence of ESBL-producing isolates ranged from 33% in *E. coli* isolated from IAIs to 39% in *E. coli* isolated from UTIs. The prevalence of *K. pneumoniae* in UTIs was 38% versus 64% in IAI isolates [34]. A multicentre retrospective study observed that the incidence of ESBL-producing *E. coli* and *Klebsiella* spp. in paediatric UTIs increased from 8% to 25% between 2001 and 2011; a strong linear correlation was apparent, with a yearly increase of 2.1% [35].

Several studies performed molecular characterisation of ESBL-producing Enterobacteriaceae [30–33,37]. The ESBL genes bla_{CTX-M} , bla_{TEM} and bla_{SHV} were commonly identified, with bla_{CTX-M} having a considerably higher prevalence compared with bla_{TEM} and bla_{SHV} , and with $bla_{CTX-M-15}$ identified as the most prevalent subtype [30–34,37]. In several of these studies, the coexistence of at least two ESBL genes in the majority of isolates was reported [30–32]. Three studies also detected bla_{OXA} genes in ESBL-producing isolates: in 30% of ESBL-positive *E. coli* from UTIs [30]; in 5.9% of Enterobacteriaceae from UTIs and IAIs [34]; and in 20–47% of *E. coli* and 23–53% of *Klebsiella* spp. isolates from inpatients across three hospitals [31].

Carbapenem-resistant Enterobacteriaceae isolates were the focus of two studies [29,36]. Of 27 *E. coli* isolates that were carbapenem-resistant phenotypically, 15 harboured bla_{OXA} carbapenemase genes (bla_{OXA-48} , $n = 13$; $bla_{OXA-181}$, $n = 2$); of the remaining 12 isolates that lacked carbapenemase genes, 9 showed

multiple deletions and truncations in the porin-encoding genes *ompC* and *ompF*. Although all isolates were resistant to ertapenem, resistance to gentamicin and imipenem was considerably lower (30% and 37%, respectively); the lowest levels of resistance were shown to meropenem (22%) and amikacin (3.7%) [29]. A retrospective case series set in a single hospital from 2011–2014 showed an increasing incidence of carbapenem-resistant Enterobacteriaceae infections, rising from a monthly mean of 0.5 cases in 2011 to 1.5 cases in 2014 [36]. Additionally, carbapenem-resistant *E. coli* was isolated from stool samples of 5/41 (12%) cancer patients [28]. In a study carried out both in Lebanon and Jordan, the presence of MBL gene type bla_{NDM} was observed in 8/307 ESBL-positive isolates, all originating from patients from Jordan [34].

A 2015 study that evaluated AMR in isolates from bacteraemia episodes in adult patients with cancer found that 10.7% and 6.7% of episodes were caused by third-generation cephalosporin-resistant *E. coli* and *K. pneumoniae*, respectively [38]. Overall, *E. coli* and *K. pneumoniae* accounted for 13 of the 22 third-generation cephalosporin-resistant GNB isolates, among which the carbapenem resistance rate was 29.3%.

Colistin-resistant Enterobacteriaceae, predominantly *E. coli* and *K. pneumoniae*, were characterised in three studies [39–41]. In each study, resistance to colistin was attributed to mutations in the *mgrB*, *pmrA/B* and *phoP/Q* genes.

3.1.3. Resistance of *Pseudomonas aeruginosa*

Antimicrobial susceptibilities and mechanisms of resistance in *P. aeruginosa* were investigated in three studies [42–44]. In patients diagnosed with *P. aeruginosa* infections (predominantly of the respiratory and urinary tracts), 29% of isolates were resistant to both imipenem and ciprofloxacin; identified risk factors for combined resistance included receiving fluoroquinolone or carbapenem antimicrobials or being hospitalised within the prior 3 months [42].

Carbapenem-resistant *P. aeruginosa* isolates susceptible only to fosfomycin and/or colistin were characterised in two studies: the MBL gene *bla*_{VIM-2} was detected in 50–75% of isolates, one study found the coexistence of AmpC, and both studies also identified isolates with *oprD* gene mutations or downregulations that were due, in part, to increased *bla*_{VIM-2} (intact *oprD* encodes a carbapenemase-selective porin) [43,44].

3.1.4. Resistance in multiple bacteria

Six studies investigated several GNB species isolated from patients with a specified disease syndrome or treatment, which included ventilator-associated pneumonia (VAP) [45], burns [46], UTIs and IAIs [47], device-associated healthcare-associated infections [48], diabetic foot ulcers [49] and tigecycline treatment [50]. In one study, substantial levels of AMR were apparent among *A. baumannii* [$n = 28$ (65%)] and *P. aeruginosa* [$n = 23$ (53%)] from VAP, with 93% and 13% of isolates classified as XDR, respectively [45]. GNB were isolated from approximately one-half of all infections in patients admitted to a burn care centre, most commonly *A. baumannii* and *P. aeruginosa* [46]. The *A. baumannii* isolates generally showed high levels of resistance (>88%) to the tested antimicrobials but not colistin; resistance in *P. aeruginosa* isolates was also considerable, with 45–60% resistance to all carbapenems and cephalosporins tested. Enterobacteriaceae were prominent isolates from deep-tissue samples of diabetic foot ulcers (42% of all isolates), 25% of which were ESBL-producing and 2% carbapenem-resistant [49]. *Pseudomonas aeruginosa* was also commonly isolated (11% of all isolates) and showed a prevalence similar to Enterobacteriaceae for carbapenem resistance (3%). *Escherichia coli* predominated among GNB isolates from UTIs and IAIs collected from hospitals in Lebanon and Jordan [47]. ESBL was detected phenotypically in 43–49% of *E. coli*, with genotypic studies detecting *bla*_{CTX-M-15} most frequently. In the 17 (1.6%) carbapenem-resistant Enterobacteriaceae isolates, *bla*_{OXA-48} and *bla*_{NDM-1} were present in 10 and 7 isolates, respectively. Although *A. baumannii* and *P. aeruginosa* isolates were less prevalent, they demonstrated low susceptibility rates to the antimicrobials tested (29–89% and 4–27%, respectively) [47]. A retrospective chart review of patients receiving tigecycline therapy reported high levels of susceptibility in GNB isolates: 82% in carbapenem-resistant *Acinetobacter* spp. and 98% and 78% in third-generation cephalosporin-resistant *E. coli* and *Klebsiella* spp., respectively [50].

Of the hospital surveys in Lebanon that evaluated antimicrobial susceptibilities over a range of GNB, two were large-scale, multisite studies [52,56]. The first study analysed susceptibility results of 55 594 GNB collected from 2011–2013. *Escherichia coli* isolates had ESBL production rates of ~30% and were highly susceptible to imipenem; in contrast, *Acinetobacter* spp. showed decreasing susceptibility to imipenem over the 3-year period, which was 15% in 2013 [52]. The second study carried out a similar survey of isolates collected from 2015–2016 and reported further decreases in the susceptibility of *E. coli*, *Klebsiella* spp. and *P. aeruginosa* to several antimicrobials compared with the 2011–2013 levels. Additionally, significant decreases in susceptibility were observed for third-generation cephalosporin-resistant Enterobacteriaceae, carbapenem-resistant Enterobacteriaceae, carbapenem-resistant *P. aeruginosa* and carbapenem-resistant *Acinetobacter* spp. ($P < 0.001$ for each) [56]. The observed ESBL production in Enterobacteriaceae was 34%. Three studies specifically evaluated carbapenem-resistant GNB isolates [51,53,54]. A large multisite study observed carbapenem resistance in 1.2% of Enterobacteriaceae, 88% of *A. baumannii* and 41% of *Pseudomonas* (encompassing *P. aeruginosa* and *Pseudomonas* spp.) during 2012; molecular characterisation of carbapenem-resistant isolates identified a 70% prevalence of the *bla*_{OXA-48} gene in Enterobacteriaceae, with a high prevalence of *bla*_{OXA-23} (98%) and *bla*_{GES-11} (92%) and a low preva-

lence of *bla*_{OXA-24} (1.4%) in *A. baumannii*, and MBL genes (*bla*_{IMP} or *bla*_{VIM}) in slightly more than 20% of *Pseudomonas* isolates [54]. A smaller, single-site study carried out during a partially overlapping time period reported a similar prevalence of these β -lactamase genes [53]. Another study measured the carbapenem resistance prevalence in GNB isolates collected in a tertiary care centre over a 9-year period (2010–2018) and observed large increases in the isolation densities of carbapenem-resistant *E. coli* [51]. Lastly, community-acquired and hospital-acquired GNB infections were compared in a study in five hospitals, revealing that ESBL-producing *E. coli* and MDR *Pseudomonas* occurred at significantly higher frequencies in hospital-acquired versus community-acquired infections ($P = 0.001$) [55].

A summary of AMR trends in Lebanon is shown in Fig. 2.

3.2. Studies in Jordan

Fifteen studies in Jordan were included in this review [57–71] (Table 2).

3.2.1. Resistance of *Acinetobacter* spp

Six of the included studies evaluated AMR in *Acinetobacter* spp. [57–62], two of which assessed critically-ill adult patients with cancer with *A. baumannii* infections treated in an ICU [61,62]. The first study reported the AMR profiles of *A. baumannii* isolates from 161 patients, with all but 5 isolates being defined as MDR, XDR or PDR [61]. The second study evaluated the clinical effectiveness of colistin therapy in a subset of 77 patients with respiratory infections caused by CRAB; although microbiological clearance was achieved in 51 treated patients, 12 of these patients had either recurrence of respiratory infection or new infections elsewhere [62]. Carbapenem resistance was also highly prevalent in *A. baumannii* isolated from critical care patients with VAP (>98%) [58] and from neonates with *Acinetobacter* spp. sepsis (90%) [57]; all carbapenem-resistant isolates in both studies were susceptible to colistin. Two articles reported year-long surveys of *A. baumannii* isolated from clinical samples, both of which found high rates of multidrug resistance (74–78%) and carbapenem resistance [59,60].

3.2.2. Resistance of Enterobacteriaceae

Six studies investigated resistance in Enterobacteriaceae species [63–68]. In two studies, ESBL-producing *E. coli* and *K. pneumoniae* isolates from patients with community-acquired UTIs were examined [63,64]. The first study included outpatients and inpatients of all ages with UTIs, finding that 42.5% of *E. coli* and *K. pneumoniae* isolates were ESBL-producers [64]. The second, a case-control study focused on children hospitalised with community-acquired UTI, identified risk factors for ESBL *E. coli* and *K. pneumoniae* that included recent use of antimicrobials, recent hospitalisation, recurrent UTI and renal anomalies [63]. In both studies, ESBL-producing isolates were highly susceptible to carbapenems, were highly resistant to third- and fourth-generation cephalosporins (96–99%), and had significant rates of resistance to several non- β -lactam antimicrobials [63,64]. A further study that evaluated ESBL-producing *E. coli* isolates predominantly from UTIs also observed this pattern of resistance [65]. In a study of 88 neonates with serious bacterial infections [68], *E. coli* and *Klebsiella* spp. were identified in 48 patients; of these isolates, 54% of *E. coli* and 68% of *Klebsiella* spp. were ESBL-producers. Overall, Enterobacteriaceae isolates tested were nearly all ($\geq 96\%$) susceptible to carbapenems but were frequently resistant (55–59%) to third- and fourth-generation cephalosporins [68]. Two studies characterised carbapenem-resistant Enterobacteriaceae [66,67]. Of 296 *K. pneumoniae* isolates from patients attending a single hospital, 7 (2.4%) were carbapenem resistant [66]; PCR screening detected the MBL *bla*_{NDM} gene in 2/7 isolates, the carbapenemase gene *bla*_{OXA-48-like}

Table 2
Studies of antimicrobial resistance (AMR) rates and mechanisms in Gram-negative bacteria (GNB) from Jordan

Article	Study period	Study population	Pathogens reviewed	Observations related to AMR	Observations related to mechanisms of resistance
Studies investigating <i>Acinetobacter</i> spp./ <i>Acinetobacter baumannii</i>					
Al-Lawama et al., 2016 [57]	2-year period (dates NR)	Patients in a level 3 neonatal unit with blood culture-confirmed sepsis due to MDR <i>Acinetobacter</i> spp. and treated with colistin	<i>Acinetobacter</i> spp. (n = 21)	During the study period, 21 newborns received colistin concomitantly with other antimicrobial and/or antifungal medications (18/21 received colistin with imipenem and amikacin/gentamicin for the duration of treatment) 19/21 <i>Acinetobacter</i> spp. isolates were carbapenem-resistant and all were susceptible to colistin 19/21 of the newborns treated survived and had a clear follow-up blood culture (range, 1–8 days for clearance)	NR
Almomani et al., 2015 [58]	Jan. 2007 to Jun. 2013	Patients aged ≥16 years admitted to a CCU with VAP caused mainly by <i>A. baumannii</i> (at a single hospital)	<i>A. baumannii</i> (n = 121)	119/121 <i>A. baumannii</i> VAP cases were caused by MDR <i>A. baumannii</i> Overall incidence rate of MDR <i>A. baumannii</i> VAP was 1.59 cases per 100 CCU admissions MDR <i>A. baumannii</i> isolates were variably resistant against 24 different types of antimicrobials tested: • Susceptibility was 0% for 9 antimicrobials, including ceftriaxone • Susceptibility to imipenem and meropenem was 0.9% and 1.8%, respectively • Highest susceptibility was to colistin (100%)	NR
Batarseh et al., 2016 [59]	Jan. 2013 to Dec. 2013	Patients at a single hospital (age not stated; 116 non-repetitive clinical samples positive for <i>A. baumannii</i>)	<i>A. baumannii</i> (n = 116)	78% of the <i>A. baumannii</i> isolates were MDR and 9% were PDR High resistance rates (97–100%) were observed for all generations of cephalosporins and imipenem Very low resistance to colistin was observed (1.7%)	NR
El-Khatib et al., 2021 [60]	Jan. 2018 to Dec. 2018	Patients (all ages) from hospitals, healthcare centres and the community with <i>A. baumannii</i> infection (n = 43)	<i>A. baumannii</i> (n = 43)	Antimicrobial susceptibilities were analysed in groups according to site of isolation: blood (n = 7), urine (n = 16) or other (e.g. ear swab, wound, sputum; n = 20) 32/43 isolates (74%) were classified as MDR: blood isolates, 42%; urine isolates, 63%; other, 95% Resistance to imipenem was 36% among urine isolates and 94% among isolates in the 'other' group; resistance to meropenem in these groups was 60% and 88%, respectively Resistance to ceftriaxone and ceftazidime was 14–33% in blood isolates, 88–92% in urine isolates and 88–89% in 'other' isolates 2 isolates (1 urine and 1 throat swab) were resistant to all antimicrobials tested, suggesting PDR	NR
Nazer et al., 2015 [61]	Jan. 2010 to Dec. 2013	Critically-ill patients with cancer (adults, mean age 56 years) with <i>A. baumannii</i> infection treated in the ICU of a single hospital (n = 161)	<i>A. baumannii</i> (n = 161)	Only 5/161 isolates were susceptible to common antimicrobials MDR <i>A. baumannii</i> : 13/161 (including resistance to cephalosporins) XDR <i>A. baumannii</i> : 142/161 (MDR and also resistant to carbapenems) PDR <i>A. baumannii</i> : 1/161 (142/161 were XDR)	NR
Nazer et al., 2015 [62]	Jan. 2010 to Dec. 2013	Critically-ill patients with cancer (aged ≥18 years) with carbapenem-resistant <i>A. baumannii</i> respiratory infections who were treated in the ICU of a single hospital and received i.v. colistin therapy (n = 89)	<i>A. baumannii</i> , carbapenem-resistant	Effectiveness of colistin treatment was analysed in 77 patients: • 51/77 (66%) had microbiological clearance; however, 3 of the patients with clearance had recurrent infections and 9 had new infections (wounds and blood); of the recurrent infections, 1 was resistant to colistin • 57/89 (64%) patients died in the ICU; death was attributed to <i>A. baumannii</i> infection in 10 patients	NR
Studies investigating Enterobacteriaceae					
Studies investigating <i>Escherichia coli</i> and/or <i>Klebsiella</i> spp.					

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Table 2 (continued)

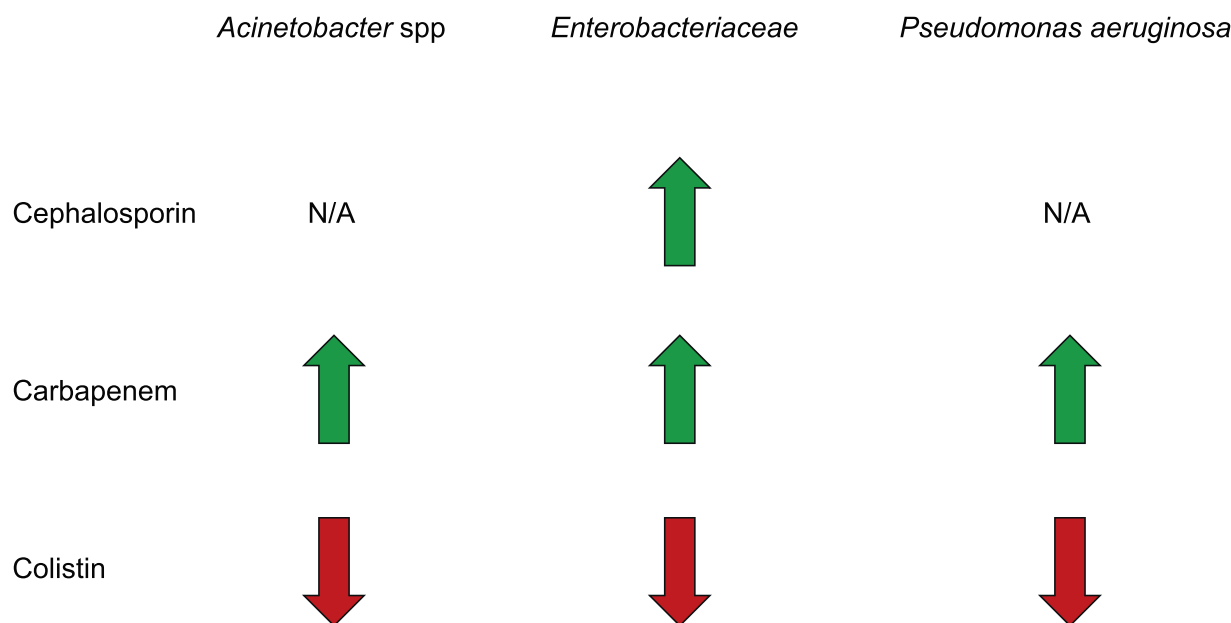
Article	Study period	Study population	Pathogens reviewed	Observations related to AMR	Observations related to mechanisms of resistance
Albaramki et al., 2019 [63]	Jan. 2012 to Jul. 2017	Hospitalised children (aged 0–18 years) with CA-UTI and positive urine culture (n = 243 patients overall)	<i>E. coli</i> (n = 132) <i>Klebsiella</i> spp. (n = 22)	<i>E. coli</i> and <i>Klebsiella</i> spp. isolates were compared in a case–control study: • ESBL-positive ‘cases’, n = 77 (<i>E. coli</i> , n = 63; <i>Klebsiella</i> spp., n = 14) • ESBL-negative ‘controls’, n = 77 (<i>E. coli</i> , n = 69; <i>Klebsiella</i> spp., n = 8) Factors significantly associated with ESBL isolates: use of antimicrobials within last 3 months, hospitalisation within last 3 months, history of recurrent UTI, renal anomalies Resistance rates for ESBL vs. non-ESBL isolates: • Third-generation cephalosporins, 99% vs. 3% • Cefuroxime, 99% vs. 40% • Carbapenems, 1% vs. 0% A third-generation cephalosporin was used empirically in 43/77 ESBL patients: 20/43 responded clinically and returned a negative urine culture; 23/43 did not improve (antimicrobial was subsequently changed) ESBL-positive, n = 251 ESBL-negative, n = 340 Incidence rate of ESBL-producing <i>E. coli</i> or <i>K. pneumoniae</i> in CA-UTI patients was 3.465 cases per 1000-patient hospital admissions; Of the ESBL-producing isolates: • Susceptibility was highest to carbapenems (96–99%) and lowest to the third- and fourth-generation cephalosporins (3–4%) ESBL-producing <i>E. coli</i> showed very high resistance rates (≥95%) to first-, second- and third-generation cephalosporins; resistance was also high against cefepime (~50%) Low levels of resistance (<10%) to carbapenems was observed Addition of amoxicillin/clavulanate enhanced the susceptibility rate of cephalosporins, particularly cefixime (86%), to a level comparable with carbapenems	NR
Almomani et al., 2018 [64]	Jan. 2015 to Dec. 2016	Outpatients, inpatients and ER patients (all ages) at a single hospital with CA-UTI caused by <i>E. coli</i> or <i>Klebsiella pneumoniae</i> (n = 591 patients)	<i>E. coli</i> <i>K. pneumoniae</i>	ESBL-positive, n = 251 ESBL-negative, n = 340 Incidence rate of ESBL-producing <i>E. coli</i> or <i>K. pneumoniae</i> in CA-UTI patients was 3.465 cases per 1000-patient hospital admissions; Of the ESBL-producing isolates: • Susceptibility was highest to carbapenems (96–99%) and lowest to the third- and fourth-generation cephalosporins (3–4%) ESBL-producing <i>E. coli</i> showed very high resistance rates (≥95%) to first-, second- and third-generation cephalosporins; resistance was also high against cefepime (~50%) Low levels of resistance (<10%) to carbapenems was observed Addition of amoxicillin/clavulanate enhanced the susceptibility rate of cephalosporins, particularly cefixime (86%), to a level comparable with carbapenems	NR
Al-Tamimi et al., 2019 [65]	Nov. 2017 to Nov. 2018	Outpatients and inpatients (all ages, predominantly adult) with suspected <i>E. coli</i> infections recruited from 2 hospitals	<i>E. coli</i> [specifically, n = 150 ESBL-producing <i>E. coli</i> from urine (87%), wound (5%), blood (1.4%) and other (6.5%)]	ESBL-producing <i>E. coli</i> showed very high resistance rates (≥95%) to first-, second- and third-generation cephalosporins; resistance was also high against cefepime (~50%) Low levels of resistance (<10%) to carbapenems was observed Addition of amoxicillin/clavulanate enhanced the susceptibility rate of cephalosporins, particularly cefixime (86%), to a level comparable with carbapenems	NR
Aqel et al., 2017 [66]	Mar. 2012 to Apr. 2013	<i>K. pneumoniae</i> isolates from patients (age not stated) attending a single hospital in Amman (n = 296)	<i>K. pneumoniae</i> (n = 296)	7/296 <i>K. pneumoniae</i> isolates were carbapenemase-producers: • All 7 isolates were resistant to carbapenems, cefotaxime and cefepime • All 7 isolates were susceptible to colistin	The 7 carbapenemase-producing isolates were screened by PCR for genes encoding CTX-M ESBLs and carbapenemase gene families <i>bla</i> _{NDM} , <i>bla</i> _{VIM} , <i>bla</i> _{IMP} , <i>bla</i> _{KPC} and <i>bla</i> _{OXA-48-like} : • 2/7 isolates were NDM-producers and contained a <i>bla</i> _{CTX-M-9-like} ESBL gene • 5/7 were OXA-48-like-producers, all of which contained either a <i>bla</i> _{CTX-M-9-like} or <i>bla</i> _{CTX-M-1-like} ESBL gene • First study to identify NDM- and OXA-48-producing <i>K. pneumoniae</i> in Jordan
Aqel et al., 2018 [67]	May 2013 to Apr. 2014	Patients (all ages) in 5 hospitals in Amman	2759 non-duplicate Enterobacteriaceae isolates of which 28 (1%) were carbapenem-resistant, including: • <i>K. pneumoniae</i> (n = 23) • <i>E. coli</i> (n = 1)	All carbapenem-resistant isolates were also resistant to cefalotin, cefoxitin, cefotaxime and ceftazidime Most (94%) were susceptible to colistin	PCR detection of carbapenemase genes <i>bla</i> _{NDM} , <i>bla</i> _{VIM} , <i>bla</i> _{KPC} and <i>bla</i> _{OXA-48-like} : • The 23 <i>K. pneumoniae</i> isolates harboured genes encoding OXA-48-like (n = 7), NDM-1 (n = 14), and both OXA-48 and NDM-1 (n = 2) • Isolates were largely not clonally related, and plasmids containing carbapenemase genes were of diverse origin

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Table 2 (continued)

Article	Study period	Study population	Pathogens reviewed	Observations related to AMR	Observations related to mechanisms of resistance
Yusef et al., 2019 [68]	Jan. 2012 to Dec. 2018	Neonates with community- or maternally-acquired serious bacterial infections admitted to a single hospital (n = 88)	GNB in 59/88: <ul style="list-style-type: none"> • <i>E. coli</i> (n = 26) • <i>Klebsiella</i> spp. (n = 22) 	39/88 patients were infected with MDR organisms, including ESBL-producing <i>E. coli</i> (n = 14) and ESBL-producing <i>K. pneumoniae</i> (n = 15) The majority of Enterobacteriaceae isolates were resistant to the third- and fourth-generation cephalosporins tested (55–59% resistant) Enterobacteriaceae isolates were most susceptible to carbapenems (≥96% susceptible)	NR
Studies investigating <i>Pseudomonas aeruginosa</i>					
Al Dawodeyah et al., 2018 [69]	Nov. 2014 to Jun. 2015	Respiratory tract samples obtained from adult patients attending the Jordan University Hospital pulmonary clinic (n = 284)	<i>P. aeruginosa</i> isolated from 61/284 patients (45/247 hospitalised; 16/37 outpatients)	32/61 (52%) <i>P. aeruginosa</i> isolates were MDR (resistant to >3 antimicrobial classes); all MDR isolates were from hospitalised patients Among all 61 isolates, susceptibility was highest to colistin (100%), cefepime (82%), ceftazidime (82%) and the carbapenems (79–80%), and lowest to cefotaxime (25%)	All 32 MDR isolates carried 1–4 of the investigated ESBL genes: <ul style="list-style-type: none"> • <i>bla</i>_{CTX-M}: 22/32 • <i>bla</i>_{TEM}: 6/32 • <i>bla</i>_{VEB-1}: 6/32 • <i>bla</i>_{GES-1}: 5/32 • <i>bla</i>_{SHV}: 4/32 • <i>bla</i>_{KPC}: 0/32 • MBL genes: <i>bla</i>_{VIM-2}, 3/32; <i>bla</i>_{IMP-1}, 0/32 All MDR isolates were positive for genes of <i>algD</i> , <i>lasB</i> and <i>toxA</i> and produced pyocyanin Among all 61 isolates, the most common virulence genes detected were <i>algD</i> and <i>lasB</i> (both 98%), <i>toxA</i> (80%), and <i>exoS</i> and <i>exoU</i> (both 33%); 87% were positive for pyocyanin The 32 MDR isolates were genotypically diverse and segregated into 14 different clusters, with no discernible relationship between genotype and AMR phenotype
Syndrome-based studies investigating several GNB species					
Hirmas et al., 2017 [70]	Jan. 2015 to Dec. 2015	Paediatric oncology patients (aged <18 years) with a positive urine culture treated at a single centre (n = 73; inpatients and outpatients)	Of all organisms detected by urine culture, GNB accounted for 84% (n = 126): <ul style="list-style-type: none"> • <i>E. coli</i>, 51% • <i>K. pneumoniae</i>, 9% • <i>P. aeruginosa</i>, 8% 	Of GNB, 37% were ESBL-producers and 3% were MDR Resistance was lowest against the carbapenems (<5%); approximately one-half of isolates were resistant to third-generation cephalosporins Among <i>E. coli</i> isolates, 53% were ESBL-producers	NR
Yusef et al., 2018 [71]	Jan. 2012 to Dec. 2015	Neonates with sepsis treated in the NICU of a single hospital (n = 68)	Among GNB (n = 42; 62% of neonates with sepsis): <ul style="list-style-type: none"> • <i>A. baumannii</i> (n = 18; 27%) • <i>K. pneumoniae</i> (n = 15; 22%) • <i>E. coli</i> (n = 4; 6%) • Other (n = 5; 7%) 	MDR-GNB pathogens included <i>A. baumannii</i> (n = 18), ESBL-producing Enterobacteriaceae [n = 14, including <i>E. coli</i> (n = 4) and <i>K. pneumoniae</i> (n = 10)] and KPC-producing <i>K. pneumoniae</i> (n = 2) <i>A. baumannii</i> were resistant to all antimicrobial groups except colistin (100% susceptible) Enterobacteriaceae (n = 21) were most susceptible to carbapenems (90%)	NR

CA-UTI, community-acquired urinary tract infection; CCU, critical care unit; ESBL, extended-spectrum β -lactamase; ER, emergency room; ICU, intensive care unit; i.v., intravenous; MBL, metallo- β -lactamase; MDR, multidrug-resistant; NICU, neonatal intensive care unit; NR, not recorded; PDR, pandrug-resistant; UTI, urinary tract infection; VAP, ventilator-associated pneumonia; XDR, extensively drug-resistant.



N/A=not available

Fig. 2. Summary of antimicrobial resistance trends in Lebanon. Red arrows indicate a decreased rate of resistance and green arrows indicate an increased rate of resistance.

in 5/7 and the ESBL *bla*_{CTX-M-9-like} or *bla*_{CTX-M-1-like} gene in 7/7 isolates. A slightly lower rate of carbapenem resistance was identified in a study of Enterobacteriaceae isolates conducted across several hospitals [67]: 28/2759 (1.0%) isolates were resistant, with *K. pneumoniae* predominating (23/28). Among the carbapenem-resistant isolates, *bla*_{NDM-1} was the most frequently detected carbapenemase gene (16/23 *K. pneumoniae* and 1/1 *E. coli*). In both studies, isolates remained highly susceptible to colistin (94–100%) [66,67].

3.2.3. Resistance of *Pseudomonas aeruginosa*

A study analysing *P. aeruginosa* isolates from respiratory tract samples of inpatients and outpatients observed complete susceptibility to colistin (100%) and lower levels of susceptibility to carbapenems and third-generation cephalosporins (~80%) [69]. Of the 45 isolates collected from hospitalised patients, 32 (71.1%) were MDR; in contrast, multidrug resistance was not identified in any of the 16 isolates originating from outpatients. Molecular characterisation of the 32 MDR isolates indicated that they were genotypically diverse and revealed a high prevalence of ESBL genes, particularly *bla*_{CTX-M} (69%), and a low prevalence of MBL genes (≤9.4%).

3.2.4. Resistance in multiple bacteria

Two studies evaluated a range of GNB isolates from paediatric patients [70,71]. Of organisms detected by urine culture in paediatric oncology patients, GNB were most prevalent (84%), particularly *E. coli* (51%). Among the 126 GNB isolates, 37% were ESBL-producers and 3% were MDR, with low resistance to carbapenems (<5%) and moderate levels of resistance to third-generation cephalosporins (~50%) [70]. GNB were also prevalent in neonates with sepsis, accounting for 62% of bacterial isolates [71]. AMR levels were high, with all *A. baumannii* and *E. coli* isolates identified as MDR. Resistance was particularly high in the *A. baumannii* isolates, in which susceptibility only to colistin (100% susceptible) was observed [71].

One study evaluated ESBL-producing *E. coli* isolates from UTIs and IAIs both in Jordan and Lebanon. The study found a significantly higher prevalence of ESBL-producing *E. coli* in Jordan com-

pared with Lebanon, both in UTIs (53% vs. 39%) and IAIs (58% vs. 33%; $P < 0.0001$ and $P = 0.0003$, respectively) [34].

A summary of AMR trends in Jordan is shown in Fig. 3.

3.3. Studies in Iraq

Twelve studies in Iraq met the criteria for inclusion in the review [72–83] (Table 3).

3.3.1. Resistance of *Acinetobacter* spp

Two of the included studies investigated AMR in *Acinetobacter* spp. [72,78]. One study assessed 127 *A. baumannii* isolates from clinical specimens, reporting very high levels of multidrug resistance (96%) and carbapenem resistance (84–88%) [72]. A second study characterised mechanisms of resistance in 120 *A. baumannii-calcoaceticus* complex isolates, 110 of which were phenotypically carbapenem-resistant [78]. The *bla*_{OXA-23-like} gene was the most frequently identified (found in 101/110 isolates) and was always associated with the presence of the insertion sequence *ISAbal1* upstream [78].

3.3.2. Resistance of Enterobacteriaceae

In total, four studies were conducted in Iraq that evaluated resistance of the Enterobacteriaceae species *E. coli* and/or *K. pneumoniae* [74,76,79,82]. Three of these studies assessed isolates from patients with UTIs or burn infections, all of which reported high levels of multidrug resistance: 74–75% in *K. pneumoniae* [74,82] and 62–88% in *E. coli* [76,82]. In general, susceptibility to carbapenems was high (91–100% across studies) and susceptibility to third-generation cephalosporins was low (<10–40% across studies). The prevalence of ESBL production determined by phenotypic testing ranged from 73–85% in *K. pneumoniae* and 65–77% in *E. coli*; correspondingly, high frequencies of the ESBL genes *bla*_{TEM}, *bla*_{SHV} and *bla*_{CTX-M} were detected by PCR testing, the rank order of which varied by species and study [74,76,82]. A single study focused on 55 carbapenem-resistant *K. pneumoniae* isolates [79], all of which were classified as MDR. Phenotypically, 53% of the isolates were

Table 3
Studies of antimicrobial resistance rates (AMR) and mechanisms in Gram-negative bacteria (GNB) from Iraq

Article	Study period	Study population	Pathogens reviewed	Observations related to AMR	Observations related to mechanisms of resistance
Studies investigating <i>Acinetobacter</i> spp./ <i>Acinetobacter baumannii</i> Al Marjania et al., 2021 [72]	NR	<i>A. baumannii</i> isolated from clinical specimens collected from patients (aged 1 month–80 years) in several hospitals in Baghdad	<i>A. baumannii</i> ($n = 127$)	Resistance was $\geq 80\%$ against 15 of the 18 antimicrobials tested, including imipenem (84%) and meropenem (88%) Very high prevalence of MDR: <ul style="list-style-type: none"> 96% (122/127) of isolates were MDR 58% (74/127) were XDR 28% (36/127) were 'possible PDR' 	Isolates were screened for toxin–antitoxin systems type II genes (<i>mazEF</i> , <i>ccdAB</i> , <i>relBE</i> , <i>mqsR</i>) and quorum-sensing genes (<i>lasIR</i> , <i>rhlIR</i>): <ul style="list-style-type: none"> No <i>maz</i>, <i>ccd</i> or <i>rel</i> genes were identified <i>mqsR</i>: 1/127 isolates <i>lasIR</i>: 2/127 isolates <i>rhlIR</i>: 3/127 isolates
Ganjo et al., 2016 [78]	Jan. 2012 to Oct. 2013	Inpatients (all ages) in 4 hospitals in the Kurdistan region of Iraq	<i>A. baumannii-calcoaceticus</i> complex ($n = 120$)	110/120 isolates were carbapenem-resistant (as assessed by disk diffusion)	In the 110 carbapenem-resistant isolates: <ul style="list-style-type: none"> <i>bla</i>_{OXA-23-like}: 101/110 (92%) <i>bla</i>_{OXA-24-like}: 4/110 <i>bla</i>_{OXA-58-like}: 0 <u>ISAbat1 analysis of all 120 isolates:</u> <ul style="list-style-type: none"> Detected ISAbat1 in 116 isolates (97%) All <i>bla</i>_{OXA-23-like}-positive isolates ($n = 101$) showed upstream ISAbat1 <u>WGS of 15 isolates:</u> <ul style="list-style-type: none"> Detected additional variants of the <i>bla</i>_{OXA-51-like} gene including <i>bla</i>_{OXA-91}, <i>bla</i>_{OXA-66} and <i>bla</i>_{OXA-69} Detected <i>bla</i>_{ADC-25-like} (a variant of the chromosomal AmpC gene) in all 15 isolates Belonged to 6 STs (including ST2) <u>PFGE of all 120 isolates:</u> <ul style="list-style-type: none"> Showed isolates were distributed over 8 clusters
Studies investigating Enterobacteriaceae Studies investigating <i>Escherichia coli</i> and/or <i>Klebsiella</i> spp. Aljanaby et al., 2017 [74]	Jul. 2016 to Jan. 2017	Inpatients (age not stated) with UTIs ($n = 141$ samples) or burns infections ($n = 144$ samples) admitted to Al-Kufa Hospital in Al-Najaf Province	<i>Klebsiella pneumoniae</i> ($n = 43$)	High resistance (91–98%) to 6 antimicrobial types, including all cephalosporins tested Moderate resistance (44–49%) to 4 antimicrobial types Lowest resistance was to imipenem (9%) According to definitions of resistance given: <ul style="list-style-type: none"> 32 strains MDR, 9 strains XDR and 2 strains PDR <u>According to phenotypic tests for ESBL production:</u> <ul style="list-style-type: none"> 35/43 ESBL-producing 8/43 non-ESBL-producing 	High prevalence of β -lactamase genes detected by PCR: <ul style="list-style-type: none"> <i>bla</i>_{TEM}: 24/43 <i>bla</i>_{SHV}: 37/43 <i>bla</i>_{CTX-M}: 22/43 <i>bla</i>_{CTX-M-1} group: 21/43 <i>bla</i>_{CTX-M-2} group: 5/43 <i>bla</i>_{CTX-M-8, -9, -25} groups: 0/43
Al-Mayahie et al., 2016 [76]	Oct. 2013 to Apr. 2014	Outpatients (all ages) with recurrent UTI attending a hospital in Al-Kut city	<i>E. coli</i> ($n = 91$)	62% of isolates were MDR, of which 48 (53%) were ESBL-positive High rate of resistance to third-generation cephalosporins (~75%) No isolate showed resistance to imipenem or meropenem Phenotypically, 59/91 (65%) isolates were confirmed ESBL-producers	<i>bla</i> _{TEM} , <i>bla</i> _{SHV} , <i>bla</i> _{CTX-M} and <i>bla</i> _{OXA} analysed, 68/91 (75%) isolates possessed ≥ 1 gene: <ul style="list-style-type: none"> CTX-M was the most prevalent ESBL type (70%; CTX-M-1 the only subtype), followed by OXA-type (33%) and SHV-type (11%) All OXA-type ESBLs detected were produced concomitantly with CTX-M-1 TEM-type was not found in any isolate 59/68 isolates that were positive for ESBL genes by PCR assay were confirmed phenotypically as ESBL-producers Of the 9 isolates not phenotypically positive for ESBL, AmpC was detected by PCR in all, and all were resistant to ceftiofloxacin; 7/9 (78%) had CTX-M-1 and OXA-type ESBL, and 2/9 (22%) had CTX-M-1 only

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Table 3 (continued)

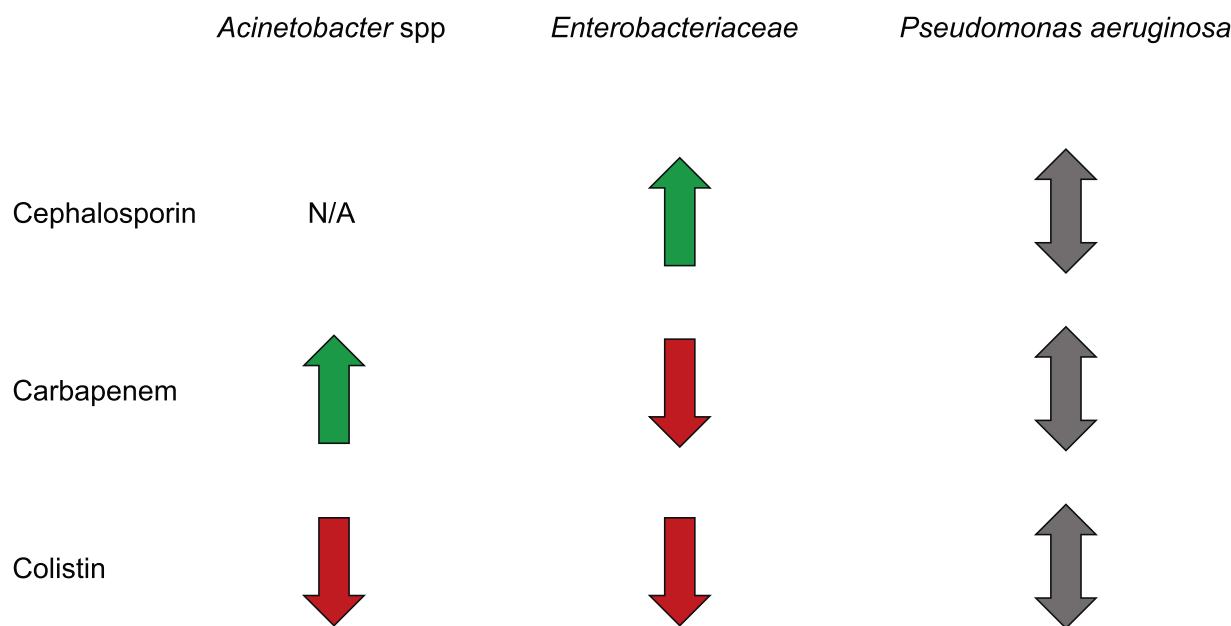
Article	Study period	Study population	Pathogens reviewed	Observations related to AMR	Observations related to mechanisms of resistance
Hussein et al., 2018 [79]	Mar. 2014 to Nov. 2015	Hospitalised patients (age not stated) in 2 Baghdad hospitals	<i>K. pneumoniae</i> (n = 55 carbapenem-resistant isolates)	All 55 carbapenem-resistant isolates were MDR: • 55/55 resistant to 11 of the 16 antimicrobials tested, including the cephalosporins • Phenotypically, 29/55 strains were identified as MBL-producing	Prevalence of MBL genes by PCR: (<i>bla</i> _{NDM-1} confirmed by sequencing) • <i>bla</i> _{NDM-1} : 37/55 (67%) • <i>bla</i> _{IMP} : 5/55 (9%) • <i>bla</i> _{VIM} : 0 • <i>bla</i> _{SIM} : 0 • <i>bla</i> _{GIM} : 0 • <i>bla</i> _{SPM} : 0
Pishtiwan et al., 2019 [82]	Jul. 2016 to Sep. 2016	Urine specimens from inpatients and outpatients (age not stated) treated at a thalassemia centre in Erbil	<i>E. coli</i> (n = 48) <i>K. pneumoniae</i> (n = 20 isolates)	88% of <i>E. coli</i> isolates and 75% of <i>K. pneumoniae</i> isolates were MDR <i>E. coli</i> and <i>K. pneumoniae</i> isolates had 100% susceptibility to imipenem and meropenem; 17–40% susceptibility to cephalosporins ESBL phenotypic testing: • 37/48 <i>E. coli</i> and 17/20 <i>K. pneumoniae</i> had positive ESBL	85% (17/20) of <i>K. pneumoniae</i> and 77% (37/48) of <i>E. coli</i> isolates were positive for ≥1 ESBL gene by PCR (all had also been positive ESBL-producers in phenotypic testing) <i>E. coli</i> isolates: • <i>bla</i> _{CTX-M} : 32% • <i>bla</i> _{SHV} : 16% • <i>bla</i> _{TEM} : 81% <i>K. pneumoniae</i> isolates: • <i>bla</i> _{CTX-M} : 41% • <i>bla</i> _{SHV} : 35% • <i>bla</i> _{TEM} : 65%
194 Studies investigating <i>Pseudomonas aeruginosa</i>					
Al-Charrakh et al., 2016 [73]	Apr. 2011 to Aug. 2011	<i>P. aeruginosa</i> isolates from clinical samples collected from patients (age not stated) in public and private hospitals in Baghdad	<i>P. aeruginosa</i> (n = 75)	6/75 (8%) isolates were imipenem-resistant, of which 4 were also meropenem-resistant and phenotypic β-lactamase-producers; these 4 isolates were also resistant to the other 8 antimicrobials tested	The 6 imipenem-resistant isolates were assayed for the MBL genes <i>bla</i> _{IMP} , <i>bla</i> _{SPM1} and <i>bla</i> _{VIM} : • 3 isolates harboured chromosomal <i>bla</i> _{IMP} • 1 isolate harboured both <i>bla</i> _{IMP} and plasmid-derived <i>bla</i> _{SPM-1} • <i>bla</i> _{VIM} was not detected
Al-Khudhairi et al., 2020 [75]	Oct. 2017 to Jan. 2018	282 adult (aged 30–70 years) patients with DFU admitted to a hospital in Al-Najaf City	<i>P. aeruginosa</i> (n = 97)	All isolates were susceptible to colistin and polymyxin B; 12% of isolates were resistant to imipenem and 41–43% to cephalosporins 12 isolates (12%) were MDR; all of these 12 isolates were MBL-producers phenotypically	Of 12 phenotypically MBL-producing <i>P. aeruginosa</i> isolates assayed: • <i>bla</i> _{VIM} : 4/12 (33%) • <i>bla</i> _{IMP} : 3/12 (25%) • <i>bla</i> _{SPM} : 2/12 • <i>bla</i> _{SIM} : 2/12 • <i>bla</i> _{NDM} : 1/12 (≥1 of the 5 genes assayed for were detected in 8 isolates; 0 genes were detected in 4 of the isolates)
Ismail et al., 2018 [80]	Not stated	Isolates (n = 100) collected from clinical samples of patients (age not stated) admitted to hospitals in Baghdad	<i>P. aeruginosa</i> (n = 22)	6/22 of the <i>P. aeruginosa</i> isolates were carbapenem-resistant and tested positive for MBL phenotypically Of the 6 carbapenem-resistant isolates, 1 isolate was PDR and 5 were MDR (including resistance to cephalosporins; susceptible to colistin)	First study to identify NDM-producing <i>P. aeruginosa</i> in Baghdad hospitals: • Of the 6 carbapenem-resistant isolates, 4 were PCR-positive for <i>bla</i> _{NDM} • Sequencing identified 3/4 as <i>bla</i> _{NDM-1} and 1/4 as <i>bla</i> _{NDM-2}

(continued on next page)

Table 3 (continued)

Article	Study period	Study population	Pathogens reviewed	Observations related to AMR	Observations related to mechanisms of resistance
van Burgh et al., 2019 [83]	Feb. 2012 to Jan. 2013	Patients (age not stated) admitted to 3 hospitals in the Kurdistan region	<i>P. aeruginosa</i> (n = 81)	XDR: 70% of isolates MDR: 86% of isolates Overall, 77–78% of isolates were resistant to cephalosporins, 56–68% to carbapenems and 4% to colistin Phenotypic testing: • 38/81 ESBL-positive, 12/81 with derepressed AmpC phenotype, 1/81 MBL-positive	WGS of 11 isolates across different phenotypes: • <i>bla</i> _{OXA-10} in 8 isolates • <i>bla</i> _{TEM-1b} and <i>bla</i> _{VEB-1} in 1 isolate • <i>bla</i> _{DHA-1} and <i>bla</i> _{OXA-10} in 1 isolate • <i>bla</i> _{PME-1} in 1 isolate Of the 11 isolates, 10 showed mutations in the <i>oprD</i> gene that likely rendered the protein non-functional, suggesting porin loss as a mechanism of carbapenem resistance Subsequent PCR assays for β -lactamase genes: Almost all isolates positive for <i>bla</i> _{OXA-50} • <i>bla</i> _{OXA-10} : 47/81 (58%) • <i>bla</i> _{VEB} : 24/81 (30%) • <i>bla</i> _{PER} : 14/81 (17%) • <i>bla</i> _{TEM} : 16/81 (20%) • <i>bla</i> _{PME} : 4/81 (5%) • <i>bla</i> _{VIM} : present in the phenotypically MBL-positive isolate No isolate was positive for <i>bla</i> _{BEL} , <i>bla</i> _{GES} , <i>bla</i> _{KPC} or <i>bla</i> _{OXA-48} WGS of the 11 isolates identified ST244 (n = 8), ST235, ST308 and ST654 (a high-risk clone) Typing experiments carried out on all isolates showed segregation into 5 highly similar clusters, indicating clonal spread had occurred
Syndrome-based studies investigating several GNB species Al-Naqshbandi et al., 2019 [77]	Jan. 2014 to Dec. 2016	Patients (age not stated) with UTI who attended a hospital in the Kurdistan region	Of 450 pathogenic isolates, 371 were GNB: • <i>E. coli</i> (n = 255) • <i>K. pneumoniae</i> (n = 76) • <i>Enterobacter</i> spp. (n = 8) • <i>A. baumannii</i> (n = 5) • Others (n = 10)	Susceptibility profiles against 25 antimicrobials were reported for each bacterial species: • Overall, GNB were highly resistant to colistin (>90% resistant) • Resistance against carbapenems varied from 86% for meropenem to 27% for ertapenem • Resistance was lowest against the third- and fourth-generation cephalosporins ceftazidime and cefepime (13% and 12%, respectively) • <i>A. baumannii</i> showed the highest resistance rates, being \geq 80% resistant to almost all antimicrobials tested	NR
Majeed and Aljanaby, 2019 [81]	Jul. to Dec. 2017	Outpatients with UTI either with CKD (n = 60 cases) or without CKD (n = 60 controls) in Al-Najaf city (aged 10–70 years)	Of 126 GNB isolates: • <i>E. coli</i> (n = 49) • <i>K. pneumoniae</i> (n = 35) • <i>P. aeruginosa</i> (n = 18) • <i>Enterobacter aerogenes</i> (n = 8)	GNB species isolated showed resistance to most antimicrobials, including third-generation cephalosporins; almost all isolates were susceptible to imipenem Higher prevalence of MDR bacteria in urine of patients with CKD (54/66) compared with control patients (42/60); there was also a higher prevalence of XDR and PDR bacteria in patients with CKD (5/66 vs. 0/60 and 1/66 vs. 0/60, respectively) Greater proportion of isolates from patients with CKD were phenotypically confirmed as ESBL-producing (21/66) compared with isolates from control patients (6/60)	There was a higher prevalence of ESBL genes in UTI isolates from patients with CKD compared with isolates from control patients In 66 UTI isolates from patients with CKD: • <i>bla</i> _{SHV} : 30/66 • <i>bla</i> _{CTX-M} : 33/66 • <i>bla</i> _{TEM} : 39/66 In 60 UTI isolates from control patients: • <i>bla</i> _{SHV} : 19/60 • <i>bla</i> _{CTX-M} : 19/60 • <i>bla</i> _{TEM} : 26/60

CKD, chronic kidney disease; DFU, diabetic foot ulcer; ESBL, extended-spectrum β -lactamase; IS, insertion sequence; MBL, metallo- β -lactamase; MDR, multidrug-resistant; NR, not recorded; PDR, pandrug-resistant; PFGE, pulsed-field gel electrophoresis; ST, sequence type; UTI, urinary tract infection; XDR, extensively drug-resistant; WGS, whole-genome sequencing.



N/A=not available

Fig. 3. Summary of antimicrobial resistance trends in Jordan. Red arrows indicate a decreased rate of resistance, green arrows indicate an increased rate of resistance and grey double-headed arrows indicate variable rates of resistance.

MBL-producers. Of the six MBL genes screened by PCR, two were detected: *bla*_{NDM-1} (67% of isolates) and *bla*_{IMP} (9% of isolates).

3.3.3. Resistance of *Pseudomonas aeruginosa*

Pseudomonas aeruginosa was the subject of four studies that found varying rates of carbapenem-resistant isolates (8–68%) [73,75,80,83]. Three of these studies focused on the characterisation of carbapenem-resistant *P. aeruginosa*, which were screened for the presence of several MBL genes; *bla*_{IMP}, *bla*_{SPM}, *bla*_{VIM}, *bla*_{SIM} and *bla*_{NDM} were all identified, although their prevalence varied between studies [73,75,80]. The fourth study observed a high level of multidrug resistance (86%) and carbapenem resistance (56–68%) in 81 *P. aeruginosa* isolates collected from patients hospitalised in the Kurdistan region [83]. Whole-genome sequencing of phenotypically representative isolates revealed a high prevalence of *oprD* gene mutations (10/11 isolates), suggesting porin loss as a mechanism of carbapenem resistance. PCR screening of the entire isolate set most frequently identified the ESBL genes *bla*_{OXA-10}, *bla*_{VEB}, *bla*_{PER} and *bla*_{TEM} (17–58% of isolates), whereas the MBL gene *bla*_{VIM} was identified in only one isolate.

3.3.4. Resistance in multiple bacteria

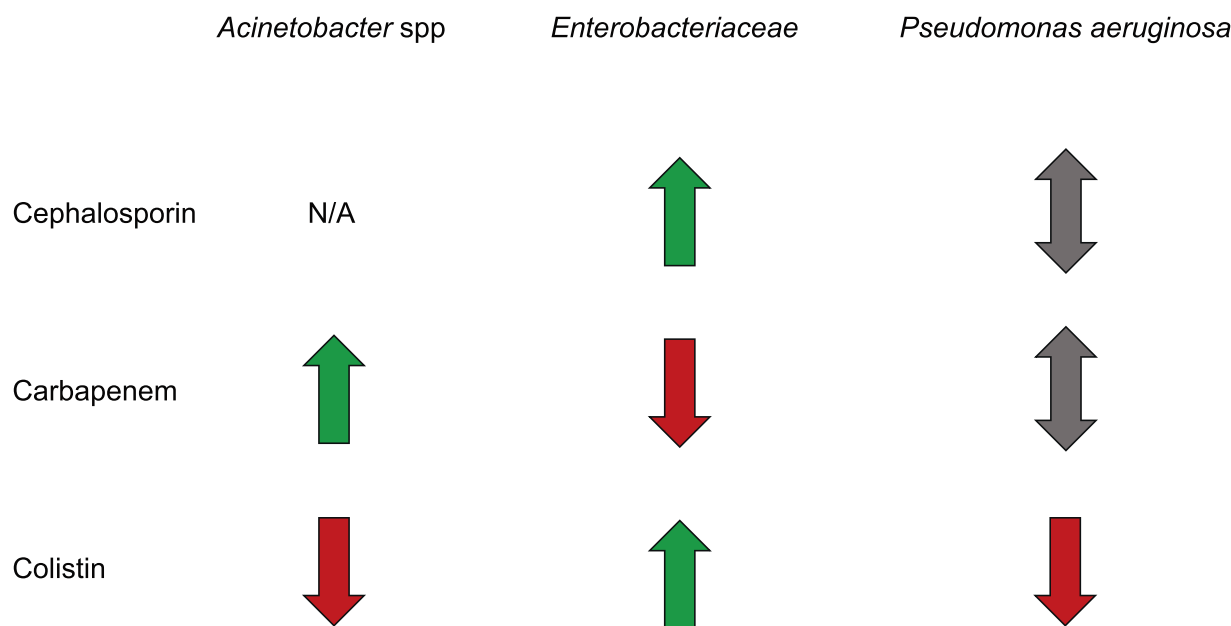
Two studies characterised several GNB species isolated from patients with UTIs [77,81]. In both studies, *E. coli* and *K. pneumoniae* were the predominant species isolated. Overall antimicrobial susceptibility profiles varied distinctly between the studies. The study in the Kurdistan region reported relatively high levels of carbapenem resistance across GNB isolates (ertapenem, 27%; imipenem, 39%; meropenem, 86%) and lower levels of resistance to third- and fourth-generation cephalosporins (12–27%) [77]; in contrast, in the study in the city of Al-Najaf, almost all isolates were susceptible to imipenem and there were higher levels of resistance to third-generation cephalosporins (25–66%) [81]. The latter study compared patients with UTI with and without chronic kidney disease, observing a higher prevalence of MDR and ESBL-positive isolates in patients with chronic kidney disease [81].

A summary of AMR trends in Iraq is shown in Fig. 4.

4. Discussion

Based on available data from Lebanon, Jordan and Iraq, there is a high prevalence of AMR that has been steadily increasing over the years. Understanding the prevalence and underlying mechanisms of resistance of emerging antimicrobial-resistant GNB, much of which coexists within the same organism, is critical and urgently needed in these countries as well as in other low- and middle-income countries [9,84].

Within Lebanon, *Acinetobacter* spp. isolates were highly resistant to carbapenems, whereas colistin resistance was relatively low [17–22,24–27]. Similar findings were observed in Jordan and Iraq, recording high rates of carbapenem-resistant *Acinetobacter* spp. isolates but lower rates of colistin resistance [57,58,72]. One study found that implementing an antimicrobial stewardship programme to help optimise antimicrobial usage resulted in a noticeable reduction in CRAB, suggesting there may be a role for antimicrobial stewardship programmes in managing AMR [85]. Studies on *Enterobacteriaceae* isolates in Lebanon again found high rates of carbapenem and cephalosporin resistance and lower levels of colistin resistance, whereas studies in Iraq found high cephalosporin and colistin resistance along with increased susceptibility to carbapenems [30,32,33,74,76,82]. Of the studies investigating *Enterobacteriaceae* isolates in Jordan, most recorded high resistance to cephalosporins along with high susceptibility to carbapenems and colistin [63–67]. Few data are available for *P. aeruginosa*; however, studies in Lebanon found that *P. aeruginosa* isolates were carbapenem-resistant and colistin-susceptible, while studies in Iraq showed varying levels of resistance to carbapenems and cephalosporins with high susceptibility to colistin, and studies in Jordan found varying levels of susceptibility to carbapenems, cephalosporins and colistin [42–44,69,75,83]. The overall trend points toward rising carbapenem and cephalosporin resistance and sustained susceptibility to colistin within this region.



N/A=not available

Fig. 4. Summary of antimicrobial resistance trends in Iraq. Red arrows indicate a decreased rate of resistance, green arrows indicate an increased rate of resistance and grey double-headed arrows indicate variable rates of resistance.

Other surrounding countries throughout Europe and the Middle East have observed similar trends in MDR-GNB [86–88].

In the studies reviewed, the most commonly observed mechanisms that GNB used for AMR were genetic modifications resulting in increased expression of antimicrobial-inactivating enzymes (i.e. ESBLs, AmpC β -lactamases and carbapenemases) and decreased permeability (i.e. mutations in genes encoding outer membrane proteins). In Lebanon and Iraq, the β -lactamase gene *bla*_{OXA-23-like} was the most frequently identified in *Acinetobacter* spp. [17,19,21,23,26,27,78]. This increase in *bla*_{OXA-23} suggests horizontal transmission of the gene within various strains of the species and could be a contributing factor to an increase in carbapenem resistance over the years, whereas the carbapenemase gene *bla*_{OXA-48-like} was most commonly identified in carbapenem-resistant *Enterobacteriaceae*. Other commonly identified *Enterobacteriaceae* ESBL genes included *bla*_{CTX-M}, *bla*_{TEM} and *bla*_{SHV}, albeit with varying rates of prevalence in Lebanon, Jordan and Iraq [30–34,37,66,69,74,76,82]. In *P. aeruginosa*, MBL genes, and more specifically *bla*_{VIM}, were identified in Lebanon and Iraq although the prevalence varied between studies [43,44,73,75,80]. Similar resistance genes are observed throughout many countries in the Middle East, Europe and Asia, suggesting a far-reaching spread of these resistance mechanisms and highlighting the need for new treatments [89–92]. A recent study investigating the use of novel carbapenem/ β -lactamase inhibitor combinations against isolates containing *bla*_{OXA-23-like} and *bla*_{OXA-48-like} genes demonstrated high efficacy both in in vitro and in vivo settings, suggesting potential for future clinical development [93].

Additional factors contributing to AMR, especially in Lebanon and Iraq, are genetic mutations in several outer membrane protein genes (*oprD*, *ompC* and *ompF*) found in *P. aeruginosa* and *E. coli* isolates [29,43,44,83]. Mutations in these genes result in decreased antimicrobial permeability as well as increased ESBL production, which is of particular concern because many of the isolates reviewed in this study already harboured high levels of ESBLs [94].

Limitations of this review include the variability of methodologies used to determine AMR, which could result in inconsistencies across studies reviewed. Additionally, the variability of anatomic sources used (i.e. urinary, respiratory, blood) may not be directly comparable. Most of the studies reviewed reported data from university hospitals, which have access to advanced molecular testing; thus, the data may be skewed towards certain geographic areas where testing equipment and resources are readily available.

Understanding phenotypic differences is no longer sufficient when treating MDR-GNB. Treatments for GNB infections must delve deeper and consider the genotype of the causative organism as well as the mechanisms of resistance. Surveillance strategies in Lebanon, Jordan and Iraq should focus on improved understanding of multidrug resistance and underlying mechanisms of resistance to advance available treatments and inform emerging trends in these and surrounding countries.

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Competing interests

JAM and MAA are employees of Pfizer and may hold stock or stock options. RAM and GMM declare no competing interests.

Ethical approval

Not required.

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