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Pandrug-resistant Gram-negative bacteria. A systematic review of current epidemiology, prognosis and treatment options.

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Abstract

Background: The literature on the epidemiology, mortality and treatment of pandrug-resistant (PDR) Gram-negative bacteria (GNB) is scarce, scattered and controversial.

Objective: To consolidate the relevant literature and identify treatment options for PDR GNB infections.

Methods: A systematic search in MEDLINE, Scopus and clinical trial registries was conducted. Studies reporting PDR clinical isolates were eligible for review if susceptibility testing for all major antimicrobials had been performed. Characteristics and findings of retrieved studies were qualitatively synthesized.

Results: Of 81 studies reviewed, 47 (58%) were published in the last 5 years. The reports reflected a worldwide dissemination of PDR GNB in 25 countries in 5 continents. Of 526 PDR isolates reported, *Pseudomonas* aeruginosa (n=175), *Acinetobacter baumannii* (n=172) and *Klebsiella pneumoniae* (n=125) were most common. PDR GNB were typically isolated in intensive care units, but several studies demonstrated wider outbreak potential, including dissemination to long-term care facilities and international spread. All-cause mortality was high (range, 20%-71%), but appeared to be substantially reduced in studies reporting treatment regimens active in vitro. No controlled trial has been performed to date, but several case reports and series noted successful use of various regimens, predominantly synergistic combinations, and in selected patients increased exposure regimens and newer antibiotics.

Conclusion: PDR GNB are increasingly being reported worldwide and are associated with high mortality. Several treatment regimens have been successfully used, of which synergistic combinations appear to be most promising and often the only available option. More

pharmacokinetic/pharmacodynamic and outcome studies are needed to guide the use of synergistic combinations.

Introduction

Mathematical prediction models estimated that thousands of extra deaths are attributable to MDR bacterial infections every year in Europe. [1] However, the mortality attributable to XDR and pandrug-resistant (PDR) infections appears to be much lower based on real-life data from a recent study in France. [1] In contrast, an alarming increase in the incidence of PDR infections, most frequently caused by PDR *Acinetobacter baumannii*, has been detected in the authors' region [2] and has been associated with high mortality. [3] In view of such controversial findings, studying the worldwide epidemiology of pandrug resistance becomes especially important. Furthermore, studies on the treatment of PDR infections are scarce and scattered [4, 5] and clinicians often resort to "salvage treatments", including the use of antimicrobial combinations or antibiotics for non-approved indications, with questionable dosing and administration route. [6]

This review aims to systematically search and consolidate the literature on the epidemiology, mortality and treatment of PDR Gram-negative bacteria (GNB). Particularly, considering the controversies described above, we examined the geographical dissemination of PDR GNB and the mortality associated with PDR GNB infections. Furthermore, the several treatment options that have been reported to be effective against PDR GNB infections were summarized and their potential to reduce mortality was assessed.

Methods

This systematic review complies with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. [7]

Search strategy: We conducted the following search in MEDLINE and Scopus, from inception to May 2019: panresistant OR panresistance OR "pan-resistant" OR "pan resistant" OR pandrug OR

pan-drug OR "pandrug-resistant" OR "pan-drug-resistant" OR "therapeutic dead end" OR "therapeutic impasse". Retrieved articles were screened for relevance based on their title and abstract. The full-text of potentially eligible articles was then reviewed. The search was supplemented by reference tracking of included papers**.** Additionally, we used the same search terms in clinical trial registries (International Clinical Trial Registry Platform, Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, Australia and New Zealand Clinical Trials Registry, International Standard Randomised Controlled Trial Number, European Clinical Trials Database) to identify trials assessing the management of PDR infections.

Eligibility criteria: We included all types of studies providing information regarding the epidemiology, prognosis and treatment of PDR GNB isolated from clinical samples in healthcare settings. We used the definition and list of antimicrobial agents proposed by Magiorakos et al [8] plus tigecycline for *A. baumannii* to define PDR. We included studies reporting at least one PDR isolate in which susceptibility testing was performed for at least one agent in each of the following antimicrobial categories (with the exception of intrinsic resistance to these agents): carbapenems, polymyxins, aminoglycosides, and glycylcyclines (tigecycline). Eligibility of non-English language studies was assessed based on their English title and abstract. When necessary, the full-text was translated in English using Google Translate.

Data items and collection process: The following data were collected: study design, country, time period, bacterial species, list of antibiotics used for susceptibility testing, criteria used to define susceptibility breakpoints, method of susceptibility testing for colistin and tigecycline, breakpoint used for susceptibility to tigecycline, number of PDR isolates, proportion PDR (of all examined isolates), treatment regimens and outcomes (both clinical and microbiological) of infections caused by PDR GNB. Reports of the same isolate in more than one studies were counted only once. Data extraction was carried out by the first author.

Exploration of the activity of newer agents: Because few relevant studies were found in our main search, we expanded the search in MEDLINE (PubMed) with the following terms: plazomicin OR eravacycline OR vaborbactam OR (avibactam AND aztreonam) OR (ceftazidime AND avibactam) OR ceftolozane. Only studies reporting the activity of these agents against GNB resistant to all other antimicrobials were included.

Risk of bias: We assessed the completeness of the list of antimicrobials used for defining PDR and the method of susceptibility testing focusing on polymyxins and taking into account that broth microdilution is the only currently recommended method [9]. In interpreting the proportion PDR, we took into account the populations studied and the fact that studies that did not report any PDR isolate were excluded from the review. We also considered the geographical distribution of possible PDR isolates from non-eligible studies. For studies reporting patient outcome, we examined the definition of outcome, the length of follow-up and whether mortality was attributable to the infection. In studies reporting treatment regimens, we recorded their design and whether patients with polymicrobial infections were included.

Synthesis of results: We conducted a qualitative presentation and synthesis of the characteristics and findings of retrieved studies. Because of substantial clinical heterogeneity, a meta-analysis was not pursued.

Results

Study selection

A flow chart of our review is depicted in Figure 1. A flow chart focused on the non-English language literature is depicted in Supplementary Figure 1.

Study characteristics

A total of 81 studies were eligible for this review, whose main characteristics are summarized in Supplementary Tables 1 to 3. The earliest study was published in 2004. Most studies (n=73; 90%) were published within the last decade; more than half (n=47) were published in the last 5 years and about a third (n=28) in the last 2 years. The proportion PDR among clinical isolates was available in 44 (54%) studies. [1, 10-51] All-cause mortality was reported in 33 (41%) [1, 4, 5, 20, 24, 35-37, 51-75] studies. Treatment regimens were reported in 26 (32%) studies. [4, 5, 24, 37, 49, 51-55, 57, 58, 60, 63-66, 68-72, 75, 76]

Definition of PDR

Susceptibility testing for the full list of antimicrobial agents as recommended in consensus definitions [8] was reported in only 6 (7%) studies. [32, 34, 40, 59, 77-79] Antimicrobials for which susceptibility testing was most frequently not reported were; fosfomycin, older generation tetracyclines (such as minocycline), aminoglycosides (missing at least one aminoglycoside), trimethoprim/sulfamethoxazole, and ampicillin/sulbactam (for *A. baumannii*) (Supplementary Table 4). Isolates with intermediate susceptibility were interpreted as non-susceptible in most studies (n=53, 65%). In 14 (17%) studies [49, 52, 54-59, 61, 63, 64, 69, 71, 80] none of the isolates had intermediate susceptibilities, while in 14 (17%) other studies [16, 17, 28, 37, 38, 43, 46, 48, 50, 51, 62, 68, 74, 81] the interpretation of intermediate susceptibility was not clarified. Broth microdilution to assess susceptibility to colistin was used in only 26 (32%) studies. [4, 10-12, 14, 15, 18, 22, 27, 29-32, 37, 42, 50, 56, 59, 61, 66, 68, 69, 78, 80, 82, 83] The EUCAST contemporary susceptibility breakpoints for tigecycline (MIC>1mg/L), were used in 13 (16%) studies, [11, 13, 18, 22, 29, 30, 33, 42, 45, 49, 52, 67, 69] while FDA breakpoints (MIC>2mg/L or FDA disc diffusion breakpoints) were used in 11 (14%) studies. [4, 16, 19-21, 23, 27, 35, 38, 43, 84] In 18

(22%) studies exact MICs were reported, [5, 49, 50, 56, 57, 59, 61, 63, 64, 66, 67, 69, 71, 77-80, 82] with almost all isolates having MICs>2mg/L.

Epidemiology of PDR

A total of 526 PDR GNB clinical isolates were reported in 25 countries in 5 continents (Table 1), reflecting a worldwide distribution. Although the ward of isolation was not reported for 59% (n=311) of all PDR isolates, at least 37% (n=194) were isolated from ICU patients. Nevertheless, several studies demonstrated the potential of PDR pathogens to cause outbreaks, involving both intra-hospital [38, 65, 73] and inter-hospital dissemination, [61] spread between hospitals and long-term care facilities, [38, 67] and international spread even to countries with a low rate of resistant pathogens. [56, 67, 79]

The most common PDR species were *Pseudomonas* aeruginosa (n=175, 33%), *Acinetobacter baumannii* (n=172, 33%) and *Klebsiella pneumoniae* (n=125, 24%). Other less common PDR pathogens included *Providencia stuartii* (n=16),[27, 65] *Serratia marcescens* (n=8), [22, 77] *Enterobacter* spp (n=6), [21] *Burkholderia* spp (n=6), [1, 21, 55] *Chryseobacterium indologenes* (n=5), [21, 54] *Elizabethkingia meningoseptica* (n=3), [21] *Morganella morganii* (n=2), [21] and *Escherichia coli* (n=1). [21]

The proportion PDR of examined isolates was highly variable (ranging from 0.01% to 21%) among reviewed studies, reflecting their heterogeneity in terms of bacterial species, geographical locations, patient populations and types of infection or culture sites. For example, PDR proportion ranged from 0.01% to 0.20% in large (>3000 patients) multicenter studies involving diverse patient populations, [13, 23, 27, 29, 31, 42, 83] but was much higher (0.65% to 11%) in studies of intensive care unit (ICU) patients, [15, 19, 28, 36, 44] and in studies that focused on MDR (3%

156 [45]), on carbapenem-resistant (5.7%, [11] 13.3%, [22] 2%, [32] 7.7% [49]), on XDR (10.8%, [20] 4.7%, [16] 6.5%,
157 [35] 17.7%, [33] 3.7% [37]), or on colistin-resistant isolates (13.9% [18]).

158 ## Prognosis of infections by PDR

159 All-cause mortality was examined in 142 patients with PDR GNB infection. [1, 4, 5, 20, 24, 35-37, 49, 51-74, 76]
160 To assess mortality in these studies the patients were followed for variable lengths of time; 28
161 or 30 days [1, 4, 5, 35, 36] or until discharge from the ward or the hospital. [24, 37, 52-57, 59, 60, 63-72, 75]
162 Summing the data from all studies, all-cause mortality in PDR GNB infection was 53% (n=75 of
163 142) but highly variable; excluding studies with < 5 patients, all-cause mortality ranged from
164 20% to 71%. [4, 5, 20, 35, 36, 51, 65, 73-75] Mortality was high irrespective of infecting pathogen or site of
165 infection, ranging from about 20% in urinary tract infections to >40% in other sites (Table 2).
166 Among the 75 reported deaths, mortality was judged by the authors to be directly attributable
167 to the infection in 11 cases, [20, 52, 56, 61, 62, 67, 71, 73, 75] but there were at least 6 deaths known to be
168 unrelated to the PDR infection [5, 57, 60, 68, 72] and for the rest of the cases this was not discussed.

169 Comparison of the mortality in PDR GNB infections to that in XDR GNB infections was possible in
170 4 small-scale studies, and mortality was substantially higher for the former in all of them (71% vs
171 55%, [20] 67% vs 57%, [36] 67% vs 30%, [35] and 36% vs 23% [5]). However, differences were not
172 statistically significant in individual studies, and confounding factors such as the severity of
173 underlying condition or comorbidities, the site of infection and use of different treatment
174 regimens used were not considered.

175 All-cause mortality was very high (43/61 patients, 71%) with treatment regimens inactive in
176 vitro, [24, 28, 39, 40, 55, 58, 73, 74, 77] but was substantially lower (19 /61 patients, 31%) with regimens that
177 were confirmed to be active in vitro, mainly involving synergistic combinations. [4, 5, 37, 52, 53, 55, 57, 58,
178 60, 63-66, 68-70, 73]

Treatment regimens

We did not find any completed or ongoing clinical trials on the treatment of PDR GNB infections. The only available data come from 26 studies, exclusively case series or case reports, involving n=105 patients; *K. pneumoniae* n=31, [5, 49, 52, 53, 57, 63, 64, 66, 68, 69, 71] *P. aeruginosa* n=45, [37, 51, 58, 60, 70, 72, 73, 75, 76] *A. baumannii* n=11, [4, 24] *Providencia stuartii* n=15, [65] *Chryseobacterium indologenes* n=2 [54], *Burkholderia cepacia* n=1. [55]. In 8 of the 26 studies, polymicrobial infections or patients with concurrent infections by other bacteria in other sites were included. [35-37, 57, 70, 73-75]

Treatment of PDR *K. pneumoniae*

Treatment regimens for PDR *K. pneumoniae* infections were reported in n=11 case series or case reports, summarized in Table 3. Four studies reported successful use of double-carbapenem combinations, either alone [5, 57, 68] or combined with colistin, [57, 66] against KPC-producing PDR *K. pneumoniae*. Notable is that in 2 of the studies successful clinical and microbiological outcomes were reported despite high MICs (128-256 mg/L) for carbapenems [5, 68] and the synergism was confirmed in vitro with time-kill assays. [68] Other effective treatment regimens were ceftazidime/avibactam [53, 63, 64] and high dose (200mg once daily) tigecycline combined with colistin and amikacin, a synergistic combination in vitro [69] (Table 3).

Treatment of PDR *P. aeruginosa*

Reports of successful treatment regimens against infections caused by PDR *P. aeruginosa* included; ceftolozane/tazobactam (C/T) in a patient with ventilator-associated pneumonia, [60] high-dose intravenous (IV) amikacin (25-50mg/kg) in one patient with intraabdominal infection and one patient with pneumonia (amikacin MIC 16mg/L), [70] and high-dose intraventricular amikacin in a case of ventriculitis (amikacin MIC=32mg/L). [58] Notable is that both patients treated with high-dose IV amikacin had renal failure and continuous venovenous

hemodiafiltration was concomitantly performed to prevent amikacin nephrotoxicity, allowing trough concentrations below 5 to 10 mg/L. [70]

Synergistic combinations may also be useful according to two studies. [73, 75] Amikacin (1g/day) with meropenem (2g q8h infused over 3 hours) resulted in both microbiological and clinical success in 4 cases of ventilator-associated pneumonia. [73] The combination was confirmed to be synergistic in vitro. [73] However, all isolates were intermediately susceptible to both amikacin (MIC 16mg/L) and meropenem (MIC 8mg/L), [73] and the high dose prolonged infusion of meropenem may explain the efficacy of the regimen. [85] In another case series, 4 of the 5 patients with various infections were cured (both microbiological and clinical cure), 3 of which were treated with different potentially synergistic colistin-based combinations. [75] However, synergism was not confirmed. [75]

Treatment of PDR *A. baumannii*

We found only one case series regarding the treatment of PDR *A. baumannii*. [4] In 10 patients with ventilator-associated pneumonia, the combination of IV colistin, high-dose IV tigecycline (200 mg loading dose followed after 12 h by 100 mg q12h), high-dose IV ampicillin/sulbactam (6/3g q8h) and inhaled colistin resulted in clinical success in 9 patients and microbiological eradication in 7. [4] All patients were concurrently receiving empirical MRSA coverage (linezolid n=8, vancomycin n=1, ceftaroline n=1), an important consideration as synergism between colistin and these agents has been described. [86-88]

Treatment of other PDR GNB

The combination of ceftazidime/avibactam (MIC=16mg/L) plus meropenem (MIC ≥ 256 mg/L) plus high doses of nebulized colistin, successfully treated a post-transplant cystic fibrosis patient with PDR bacteremic *Burkholderia cepacia* infection. [55] Ceftazidime/avibactam was synergistic in

vitro with meropenem, [55] which is in agreement with another case report in PDR *K. pneumoniae*. [64]

Another case series of ICU patients with bloodstream or urinary tract infections by PDR *Providencia stuartii*, evaluated the combination of piperacillin/tazobactam (4.5 g q8h) plus amikacin (1 g q24h), a synergistic combination in vitro. [65] Follow-up cultures were sterile in all but one patient, but mortality was high (6 of the 10 patients with bacteremia and 1 of the 5 patients with urinary tract infection died). [65]

In vitro activity of newer agents

In vitro activity of newer agents against PDR isolates was reported in few studies; Ceftolozane/tazobactam (C/T) was active against all 7 PDR *P. aeruginosa* isolates in 3 studies, [12, 42, 60] whereas all 14 isolates in 4 other studies were resistant to C/T. [10, 31, 83, 89] Aztreonam/avibactam was active against 2 PDR and all XDR (n=111) Enterobacteriaceae in one study. [23] Ceftazidime/avibactam was active against selected PDR strains based on case-reports (n=4 KPC-producing *K. pneumonia*, [53, 59, 63, 64], n=1 *Burkholderia cepacia* [55]). Meropenem/vaborbactam was not active against the single PDR isolate (*Providencia stuartii*) in one study. [27] Finally, plazomicin was initially reported to have good activity (MIC≤2mg/L) against 8 of 9 PDR Enterobacteriaceae in a study in Greece, [45] but in a subsequent study in the same region, 7 of 17 PDR *K. pneumonia* isolates were highly resistant to plazomicin (MIC>256mg/L), n=7 were susceptible (≤2mg/L) and n=3 had an MIC of 4mg/L. [11]

Discussion

Summary of main findings

Despite the rarity of pandrug resistance, reviewed studies reflected an increasing worldwide dissemination of PDR GNB in at least 25 countries in 5 continents. PDR GNB were mostly reported in ICU patients but significant outbreak potential and dissemination was demonstrated, including international spread. Among PDR pathogens detected by this review *A. baumannii*, *K. pneumonia* and *P. aeruginosa* were the most common species reported as PDR, whereas PDR *E. coli* remain exceedingly rare.

All-cause mortality in patients with PDR GNB infection is high. Although the extent of attributable mortality was unclear, reviewed studies indicated that mortality might be substantially reduced by treatment regimens active in vitro. Newer agents, such as ceftolozane/tazobactam, ceftazidime/avibactam and plazomicin, appear to be active against some GNB strains resistant to all older antimicrobials. [11, 12, 42, 45, 53, 59, 60, 63, 64] However, strains pan-resistant even to the newer agents have been reported. [10, 11, 31, 45, 83, 89] Other options for the treatment of PDR GNB infections include synergistic combinations [4, 5, 55, 57, 65, 68, 69, 73, 75] and increased exposure treatment regimens to achieve pharmacokinetic/pharmacodynamic (PK/PD) targets. [58, 70] However, current evidence remains limited, the risk of bias is high and head-to-head trials of different treatments are lacking.

Synergistic combinations for PDR infections

Several synergistic combinations have been successfully used in PDR GNB infections, such as double-carbapenem [5, 57, 68] or double-carbapenem with colistin [57, 66] for KPC-producing *K. pneumoniae*, ceftazidime/avibactam with carbapenems for *K. pneumoniae* [64] and *Burkholderia cepacia*, [55] and high-dose ampicillin/sulbactam with meropenem and colistin for *A. baumannii*. [4,

[90, 91] Notable is that neither double-carbapenem nor ceftazidime/avibactam are active against metallo-β-lactamases (MBLs). This has important implications considering that a significant percentage of carbapenem-resistant isolates in some areas are MBL-producers [11, 92-94]. In contrast, the combination aztreonam/avibactam can restore activity against MBL-producing isolates, [95, 96] since aztreonam is not hydrolyzed by MBLs and avibactam effectively inhibits other beta-lactamases (including ESBLs, KPC and OXA-48) therefore restoring the activity of aztreonam. Aztreonam/avibactam is not currently available, however the combination of ceftazidime/avibactam plus aztreonam has been used successfully against infections by MBL-producing bacteria. [97-99]

Other less studied combinations may also be useful. Notable is the in vitro synergy of colistin with agents such as linezolid, vancomycin and teicoplanin in colistin-resistant GNB strains. [86, 87] Fosfomycin combined with meropenem also appears promising and high cure rates (7 of 10 patients) have been reported even for fosfomycin-resistant isolates. [100] Despite the availability of several in vitro studies on synergistic combination, in vivo studies, such PK/PD and outcome studies, are lacking. [101]

Revival of old antibiotics

The emergence of MDR/XDR bacteria has led to the revival of older antibiotics, with colistin being a good example. [102] In PDR infections, colistin is often used in synergistic combinations with other antibiotics. [4, 57, 66, 72] Nebulized colistin, allowing higher epithelial lining fluid concentrations than IV colistin, [103, 104] may be useful for PDR respiratory infections and has been used as part of synergistic combinations. [4] However, data on PDR infections to allow comparison of inhaled versus IV colistin are lacking. Based on the available data from colistin-susceptible infections, adding nebulized colistin to IV colistin has been associated with improved outcomes

[105-107] and the efficacy of nebulized colistin (without concomitant IV colistin) either as monotherapy or in combination with other antibiotics has been found similar to IV colistin and has been associated with lower nephrotoxicity. [108, 109]

Another old antibiotic of renewed interest is IV fosfomycin. Although largely unavailable outside Europe, IV fosfomycin appears to be an effective treatment options for antibiotic-resistant Enterobacteriaceae, [110, 111] and has been used successfully for infections resistant to all other options. [101, 112] However, we noted a lack of reporting of fosfomycin susceptibility in several studies in this review (Supplementary Table 4). Furthermore, there are concerns regarding the in vivo activity of fosfomycin against *P. aeruginosa* (even when susceptible in vitro) and the risk of emergence of resistance during treatment. [113] Minocycline has also been proposed as an option for resistant bacteria [114] but susceptibility data for minocycline was not reported in most of the reviewed studies (Supplementary Table 4). To guide the use of these old antimicrobials in clinical practice more evidence is required from modern PK/PD studies and randomized controlled trials. [102, 115, 116]

Reconsideration of the PDR definition

Until recently, isolates with intermediate susceptibilities were interpreted as non-susceptible. [8] In 2019, EUCAST replaced the term “intermediate” with “susceptible, increased exposure” to indicate that there is high likelihood to achieve therapeutic success by increasing exposure to the antimicrobial. For example, high-dose prolonged infusion meropenem may be effective for *K. pneumoniae* with MIC 4-8mg/L. [85] Additionally, two studies on PDR *P. aeruginosa* infection demonstrated successful treatment using higher doses of amikacin. [58, 70] Another point to consider when defining PDR is the potential synergism between agents that are inactive alone but active when used in combination.

Limitations

Reported PDR proportions in this review may be overestimated because we excluded studies reporting no PDR isolate and because the list of antimicrobials tested for susceptibility was incomplete in several studies (Supplementary Table 4). In contrast, the use of methods other than broth microdilution for the evaluation of susceptibility to colistin may result in underestimation of the proportion PDR because these methods result in a high rate of false susceptibility. [117, 118]

Furthermore, although our findings indicate the worldwide spread of PDR GNB, they do not accurately reflect their geographical distribution. Most non-eligible studies originate from Asia, mainly from China (Supplementary Tables 5 and 6), resulting in underrepresentation of these areas in this review. Additionally, we cannot exclude the possibility of over-reporting or under-reporting PDR GNB in some countries.

Finally, despite our efforts to decrease language bias using Google Translate, data extraction could be inaccurate. [119] Nevertheless, for studies requiring full-text review using Google Translate we believe that their exclusion was reliable as it was based on the list of agents used for susceptibility testing.

Conclusions

PDR GNB isolates are increasingly being reported worldwide and several studies have demonstrated their potential for intra- and inter-institutional and even international dissemination. All-cause mortality following PDR GNB infection appears to be high irrespectively of the infecting organism, but the extent to which mortality is attributable to the infection remains unclear. Despite the lack of controlled trials several treatment regimens have been

reported to be effective against PDR GNB infections and the reviewed studies indicated that mortality might be substantially reduced by treatment regimens active in vitro. These include newer agents and increased exposure regimens, but most studies reporting successful treatment of PDR GNB infections used synergistic combinations. Synergistic combinations are often the only treatment option for PDR GNB infections and therefore more research is required, including PK/PD and outcome studies. Considering the rarity of the PDR GNB, multi-center studies are necessary.

Transparency declarations

Conflict of interest: None to declare

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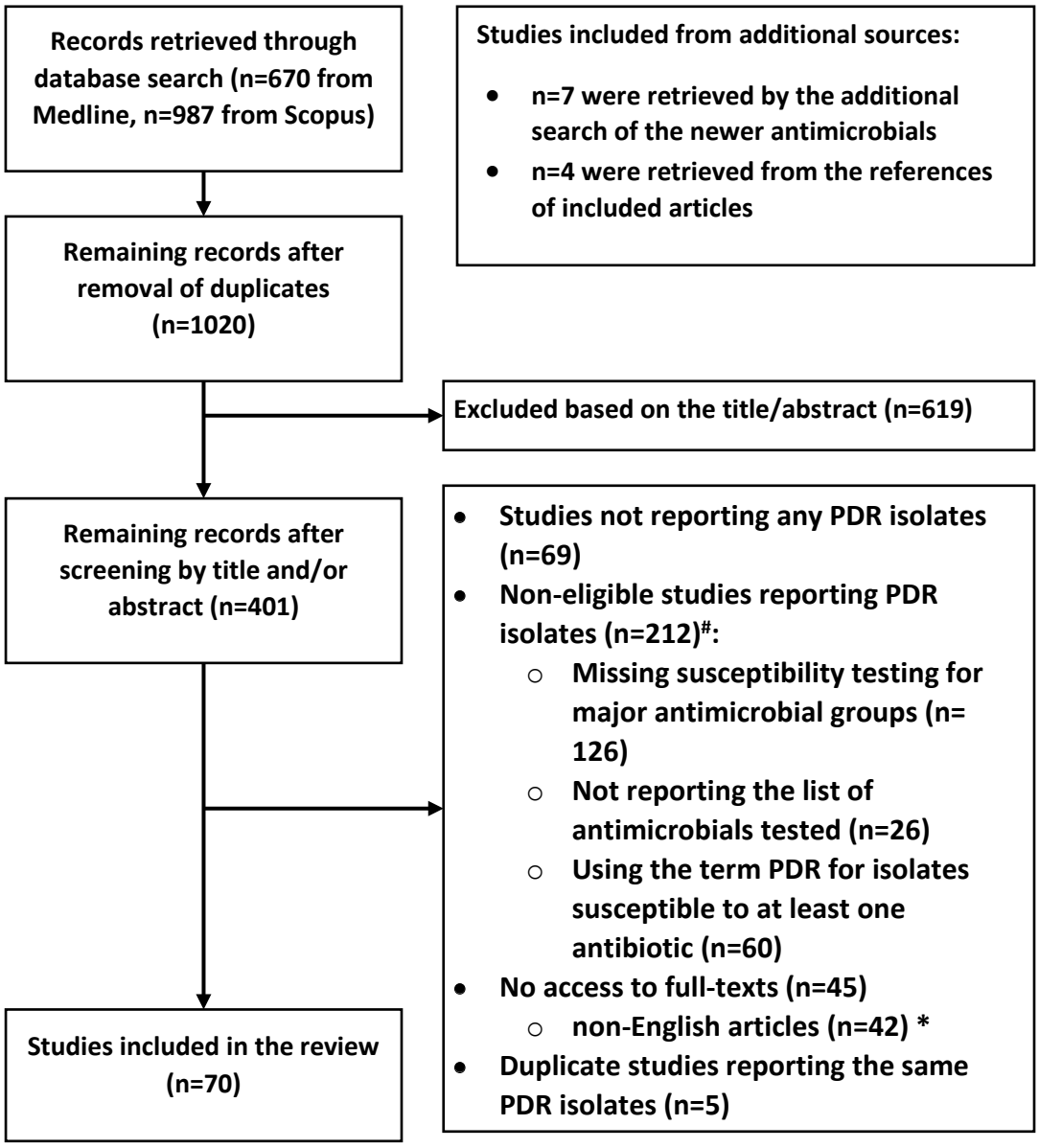
Figure 1: Flow chart of the review



PDR=pandrug resistant

* See Supplementary Figure 1 for the flow chart of the review of non-English literature

Summarized in Supplementary Tables 5-7

Table 1; Geographical distribution of pandrug-resistant isolates by species

	Total	*A. baumannii*	*K. pneumoniae*	*P. aeruginosa*	Other
Total	**526***	**172**	**125**	**175***	**54**
Europe	**280**	**107**	**71**	**80**	**22**
Greece	181	100	47	17	*Providencia stuartii* n=16 Enterobactereaceae not specified n=1
Spain	50	5	1	43	*Burkholderia cepacia* n=1
Italy	15	1	9	5	0
France	13	0	7	4	*Burkholderia cepacia* n=2
Slovakia	8	0	0	8	0
Germany	3	1	0	0	*Serratia marcescens n=2*
Belgium	2	0	0	2	0
Serbia	1	0	0	1	0
Netherlands	6	0	6	0	0
Portugal	1	0	1	0	0
Americas	**24**	**2**	**12**	**8**	**2**
United States	9	0	5	2	Enterobacteriaceae not specified n=2
Brazil	12	2	7	3	0
Mexico	2	0	0	2	0
Canada	1	0	0	1	0
Asia	**180**	**63**	**41**	**52**	**24**
India	101	11	28	40	22 #
Turkey	11	1	7	1	Enterobacteriaceae not specified n=2
Russia	3	3	0	0	0
Pakistan	29	19	2	8	0
Iran	18	17	0	1	0
Thailand	12	12	0	0	0
United Arab Emirates	4	0	4	0	0
Taiwan	1	0	0	1	0
Japan	1	0	0	1	0
Australia	**35**	**0**	**1**	**34**	**0**
Australia	35	0	1	34	0
Africa	**6**	**0**	**0**	**0**	**6**
South Africa	6	0	0	0	*Serratia marcescens* n=6

* The source (country) of one PDR *P. aeruginosa* isolate from a multi-center study was not reported.[42]

E. coli n=1, *Enterobacter* spp n=6, *Burkholderia* spp n=3, *Elizabethkingia meningoseptica* n=3, *Chryseobacterium indologenes* n=5, *Morganella morganii* n=2, unclear n=2

Table 2; All-cause mortality[1] of patients with pandrug-resistant infections by bacterial species and site of infection[2]

	Percentage of deaths (number of deaths/ total number of patients)						
	All sites	BSI[3]	RTI[4]	UTI without BSI	CNS[5]	Osteomyelitis	IAI[6]
Total	53% (75/142)	50% (21/42)	44% (19/43)	23% (3/13)	75% (3/4)	67% (2/3)	50% (1/2)
Pseudomonas aeruginosa	58% (30/52)	56% (5/9)	31% (4/13)	0% (0/1)	50% (1/2)	No data	0% (0/1)
Klebsiella pneumoniae	47% (16/34)	31% (5/16)	50% (1/2)	29% (2/7)	100% (1/1)	67% (2/3)	100% (1/1)
Acinetobacter baumannii	56% (20/36)	71% (5/7)	50% (14/28)	No data	100% (1/1)	No data	No data
Providencia stuartii	47% (7/15)	60% (6/10)	No data	20% (1/5)	No data	No data	No data

[1]Mortality was variably defined in included studies (28- or 30-day mortality, mortality up to discharge from the ward, mortality up to discharge from the hospital). [2] In some studies it was not possible to extract data for each site of infection. [3] Bloodstream infections (BSI) including; primary BSI, catheter-related BSI, BSI secondary to UTI (urinary tract infection) and BSI secondary to cellulitis. [4] Respiratory tract infections (RTI) including pneumonia and ventilator-associated pneumonia. [5] Central nervous system infections (CNS), [6] Intraabdominal infections (IAI)

Table 3; Studies of treatment options for PDR *K. pneumoniae*

	Study description		Treatment regimen	Outcomes
Double-carbapenem combinations (± colistin)	Oliva A et al 2014 [68]	Case series of 3 patients in Italy with BSI.	Case 1 and 3: 2 g of meropenem q8h plus 1 g of ertapenem q24h. Case 2: 500 mg of ertapenem q24h and 1 g of meropenem q12h (doses adjusted to creatinine clearance).	Case 1: "complete recovery" after 21 days of treatment. Case 2: "The patient became afebrile after 48 h of treatment and blood cultures were sterile. However, he died 2 days later due to acute heart failure." Case 3: complete recovery after 24 days of treatment.
	Souli M et al 2017 [5]	Case series of 14 patients in Greece. UTI n=3, sBSI due to UTI n=2, sBSI due to PN n=1, BSI n=5, VAP n=1, CRBSI n=1, EVD n=1.	1 g of ertapenem (1-hour infusion) q24h administered 1 h prior to the first dose of meropenem which was given at a dose of 2 g q8h (3-hour infusion) or equivalent renally adjusted doses.	Clinical and microbiologic outcome was evaluated on days 14 and 28 and patients were followed up to discharge. n=11 responded clinically and n=10 responded both clinically and microbiologically. n=9 were alive at last follow-up.
	Oliva A et al 2015 [66]	Case report of a bloodstream infection (both urine and central venous catheter cultures were also positive). Italy.	ertapenem 1 g/day + meropenem 2 g q8h + IV colistin (loading 6 MIU, then 4,5 MIU q12h). The triple combination (ertapenem, meropenem, colistin) was found to be more rapidly bactericidal compared to double-carbapenem alone in time-kill assays.	"After 96 h she became afebrile. Laboratory analyses showed a reduction of the ESR and CRP. Blood and urine cultures did not grow any organism". The patient was discharged after 14 days
	Emre S et al 2018 [57]	Report of 2 patients in Turkey. One with soft tissue infection and one with catheter related bacteremia.	Case 1: meropenem 1g x3 + ertapenem 1g x1 + colistin 9 MIU loading dose followed by 4.5 MIU q12h. Case 2: meropenem 1g x3 + ertapenem 1g x1	In both patients repeat cultures were sterile. The first patient died at day 32 (not attributable to the infection). The second patient was followed up to day 77 (cured)

Regimens based on ceftazidime/avibactam	Parruti G et al 2019 [53]	Case report. Italy. Recurrent bacteremia secondary to vertebral osteomyelitis associated with prosthetic material.	The final regimen included: ceftazidime/avibactam (2g/8h), tigecycline (loading 100mg then 50mg/12h), meropenem (2g/8h), gentamycin (loading 7mg/kg, then 5mg/kg/24h)	Repeated recurrences despite transient response and removal of the prosthetic material. The patient finally responded to treatment including ceftazidime/avibactam.
	Mandrawa CL et al 2016 [63]	Case report from Australia. Severe pancreatitis complicated by IAI by PDR *K. pneumoniae*	Ceftazidime/avibactam (plus metronidazole and teicoplanin). The isolate (KPC2-producing) was susceptible in vitro to ceftazidime/avibactam.	The patient demonstrated a clinical, biochemical and radiological response with no development of in vitro resistance after 6 weeks of treatment. However, microbiological clearance was not achieved, surgical management was not possible, and the patient died soon.
	Camargo JF et al 2015 [64]	Case report from USA. BSI. Also isolated from urine at $>10^5$ CFU/mL and the central venous catheter tip ($>10^2$ CFU/mL).	Ceftazidime/avibactam (1g/250 mg q8h and ertapenem (1 g q24h)(doses adjusted for creatinine clearance). Of note is that the patient had previously failed a triple regimen (meropenem, ertapenem, colistin). The isolate was susceptible in vitro to ceftazidime/avibactam alone and synergy was noted with carbapenems.	The patient responded well, with sterilization of blood cultures within 24 hours. She was discharged from the intensive care unit after 2 weeks of treatment.

Other treatment regimens	Humphries RM et al 2010 [69]	Case report. USA. CBSI. MICs: colistin >8mg/L, carbapenems >16mg/L, amikacin 32 mg/L, tigecycline 2mg/L	IV (10.5 MIU q24h) and inhaled (2.25 MIU q12h) colistin, high-dose tigecycline (200 mg IV daily) and IV amikacin (500 mg q12h for 10 days). Of note is that the patients had not responded to a combination regimen including standard dose tigecycline (50mg twice daily). Both tigecycline + amikacin and tigecycline + colistin were found to be synergistic in checkerboard assays.	The patient improved clinically and was discharged after 75 days. The bacteremia resolved but the patient remained colonized (rectal swab and sputum cultures)
	Trevino M et al 2011 [49]	Case report (only n=1 PDR infection). Spain. Bacteremia.	Case 1: First tigecycline 50mg q12h (MIC=1mg/L). Then fosfomycin 4g q8h (MIC=192mg/L) + amikacin 500mg q12h (MIC=32mg/L).	"Failure and still in hospital"
	Alho AC et al 2019 [52]	Case report. Portugal. BSI secondary to osteomyelitis. Patient with acute lymphoblastic leukemia.	Colistin 5 MIU q12h (dose increased from 4 MIU which had been given for 12 days), tigecycline 200mg loading followed by 100mg q12h, meropenem 2g q8h, amikacin 1g q24h. MICs were not reported.	The patient died with persistent bacteremia
	Elemam A et al 2009 [71]	Case report. USA. Case 1: catheter-related UTI. Case 2: sBSI associated with a post-Whipple hepatic abscess	Case 1: catheter removal and tigecycline for 10 days (MIC>8mg/L). Case 2: abscess drainage and tigecycline + colistin (doses not reported)	Case 1: Persistent dysuria at discharge. Spontaneous resolution of symptoms but persistent bacteriuria 1 year later Case 2: Died of septic shock at day 14

BSI= bloodstream infection, CRBSI=catheter-related bloodstream infection, CRP= C-reactive protein, ESR= erythrocyte sedimentation rate, EVD=external ventricular drainage, IAI= intraabdominal infection, MIU= million international units, IV= intravenous, PN= pneumonia, sBSI= secondary bloodstream infection, UTI= urinary tract infection, VAP=ventilator-associated pneumoniae

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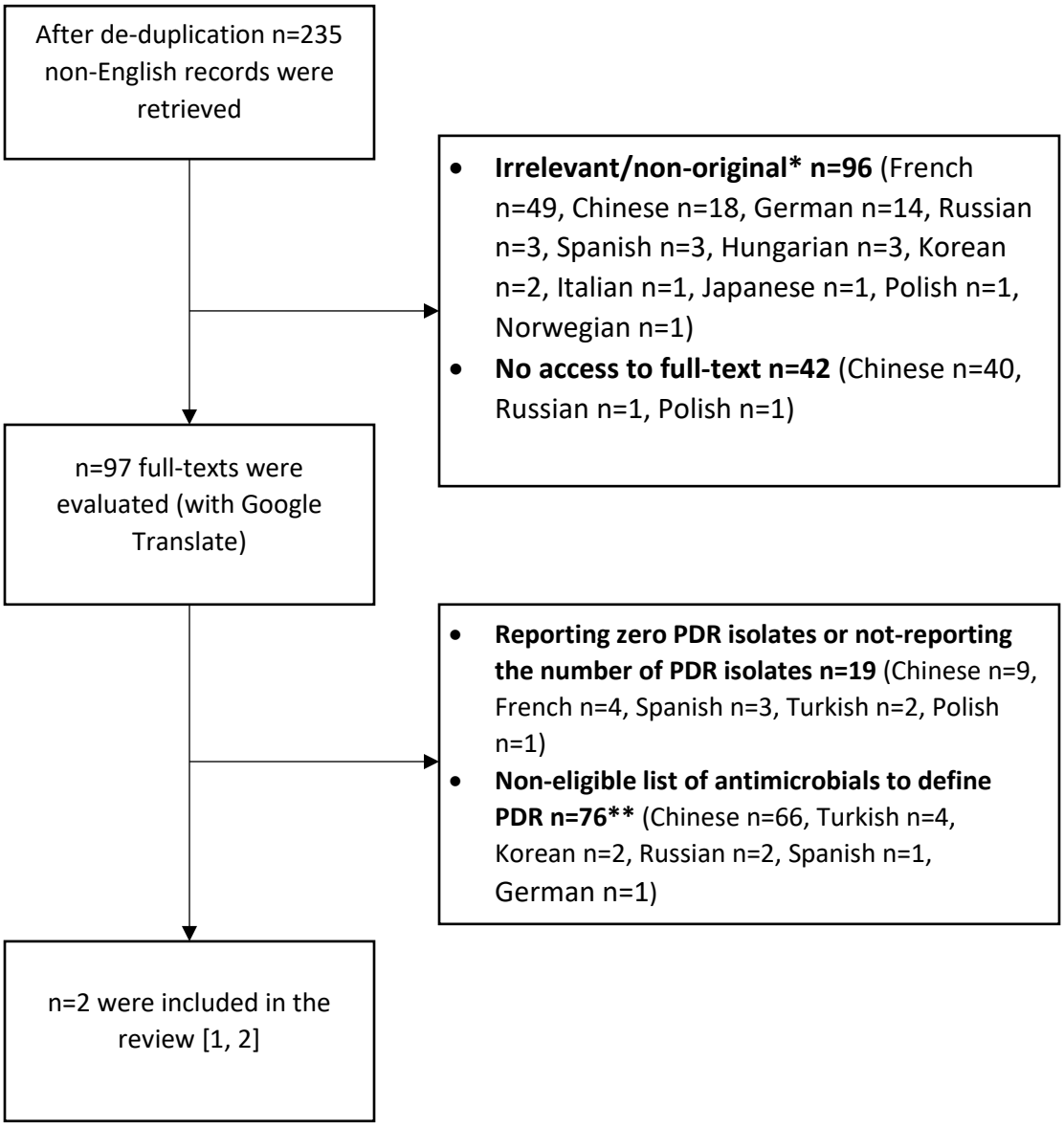

*Such as reviews and commentaries not providing original data. **Summarized in Supplementary Tables 5-7. PDR=pandrug resistant

Supplementary Table 1; Studies providing information regarding the proportion of pandrug resistance

First Author-publication year	Study year/ period	Country	Single center/ multicenter	Outpatient / inpatient	Healthcare setting	Type of infection	Pathogens studied[1]
Del Barrio-Tofiño E 2019 [3]	2017	Spain	Multicenter	Mixed	51 hospitals	Clinical isolates	*P. aeruginosa*
Galani I 2019 [4]	2014-2016	Greece	Multicenter	Unclear	15 public and private tertiary- and secondary-care hospitals	Clinical isolates	Carbapenem-resistant *K. pneumonia*
Gherardi G 2019 [5]	2010-2016	Italy	Single center	Mixed	Cystic fibrosis center	Clinical isolates from respiratory tract specimens	*P. aeruginosa*
Le Page 2019 [6]	2014-2016	France	Multicenter	Mixed	4 University Hospitals	Clinical isolates	*E. coli*, *K. pneumoniae*, *P. aeruginosa*, *A. baumannii*
Perez A 2019 [7]	2012-2015	Spain, Italy, Greece	Multicenter	Inpatients	12 Hospitals	VAP	*P. aeruginosa*
Abat et al 2018 [8]	2009-2015	France	Multicenter	Mixed	4 University hospitals	Clinical isolates	*XDR P. aeruginosa*, *A. baumannii*, *S. maltophilia*, *K. pneumoniae*, *B. cepacia*

First Author-publication year	Study year/ period	Country	Single center/ multicenter	Outpatient / inpatient	Healthcare setting	Type of infection	Pathogens studied[1]
Álvarez-Lerma et al 2018 [9]	2007-2016	Spain	Multicenter	Inpatients	Intensive care units	Device-associated infections (VAP, CRBSI, CAUTI)	*P. aeruginosa*
Ansari M et al 2018 [10]	2015-2016	Pakistan	Single center	Unclear	Military hospital	Clinical isolates	Carbapenem-resistant *K. pneumoniae*
Arumugam SN et al 2018 [11]	2012-2015	India	Multicenter	Unclear	Tertiary hospitals	Clinical isolates	*P. aeruginosa*
Braun G et al 2018 [12]	2009-2015	Brazil	Single center	Unclear	Tertiary hospital	Bacteremia	polymyxin-resistant *K. pneumoniae*
Durdu et al 2018 [13]	2012-2015	Turkey	Single center	Inpatients	5 large ICUs of a university hospital	ICU-acquired infections	Gram-negative
Katsiari et al 2018 [14]	2011-2016	Greece	Single center	Inpatients	Intensive care unit	bacteremia with sepsis	XDR *A. baumannii*
Mohapatra et al 2018 [15]	2013-2017	India	Single center	Unclear	Tertiary hospital	Clinical isolates	Gram-negative
Pedersen T et al 2018 [16]	2012-2013	South Africa	Multicenter	Inpatients	10 private hospitals	Clinical isolates	Carbapenem-resistant Enterobacteriaceae
Sader HS et al 2018 [17]	2016	USA	Multicenter	Unclear	84 medical centers	Clinical isolates associated with infection	Enterobacteriaceae
Xiao J et al 2018 [18]	2006-2018	Italy	Single center	Inpatients	Teaching hospital	Meningitis in children	*A. baumannii*

First Author-publication year	Study year/ period	Country	Single center/ multicenter	Outpatient / inpatient	Healthcare setting	Type of infection	Pathogens studied[1]
Aguilar-Rodea P et al 2017 [19]	2007-2013	Mexico	Single center	Inpatients	Pediatric tertiary hospital	Nosocomial infections	*P. aeruginosa*
Aykac K et al 2017 [20]	2012-2017	Turkey	Single center	Outpatient	Tertiary hospital (pediatric patients)	Nosocomial bloodstream or central nervous system infections	Gram-negative
Castanheira M et al 2017 [21]	2014	31 countries; United States, Europe, Latin America and Asia-Pacific	Multicenter	Mixed	82 hospitals	Clinical isolates	Gram-negative
Khan ID et al 2017 [22]	2014-2016	India	Single center	Inpatients	Intensive care unit	Device-associated infections (VAP, CRBSI,CAUTI)	*K. pneumoniae*, *E. coli*, *P. aeruginosa*, *B. cepacia*, *A. baumannii*
Pfaller MA et al 2017 [23]	2012-2015	17 European countries plus	Multicenter	Inpatients	Hospitalized patients- 41 medical centers	Urinary tract or intra-abdominal infections	Enterobacteriaceae *P. aeruginosa*

First Author-publication year	Study year/ period	Country	Single center/ multicenter	Outpatient / inpatient	Healthcare setting	Type of infection	Pathogens studied[1]
		Turkey and Israel					
Sheck EA et al 2017 [24]	2013-2014	Russia	Multicenter	Inpatients	Hospitals	Nosocomial clinical isolates	*A. baumannii*
Shortridge D et al 2017 [25]	2012-2015	USA	Multicenter	Unclear	32 medical centers	bloodstream infections, pneumonia, skin and skin structure infections, urinary tract infections, intra-abdominal infections, and other types of infections	*P. aeruginosa*
Zafari M et al 2017 [26]	2015-2016	Iran	Single center	Mixed	University hospital	100 randomly selected clinical isolates	carbapenem-resistant *A. baumannii*
Bathoorn E et al 2016 [27]	2013-2014	Greece	Multicenter	Inpatients	3 hospitals	Randomly selected clinical isolates	KPC *K. pneumoniae*
Shokri D et al 2016 [28]	2013-2014	Iran	Multicenter	Unclear	University hospital	Clinical isolates	*P. aeruginosa*
Tsioutis C et l 2016 [29]	2012-2015	Greece	Single center	Inpatients	Intensive care unit	VAP	XDR *A. baumannii*
Inchai J et al 2015 (two publications from the same cohort) [30, 31]	2005-2011	Thailand	Single center	Inpatients	Intensive care unit	VAP	*A. baumannii*

First Author-publication year	Study year/ period	Country	Single center/ multicenter	Outpatient / inpatient	Healthcare setting	Type of infection	Pathogens studied[1]
Kulkova N et al 2015 [32]	2011-2012	Slovakia	Single center	Inpatients	University hospital	Bacteremia	Carbapenem resistant Gram- negative
Oikonomou O et al 2015 [33]	2012-2014	Greece	Single center	Unclear	University hospital	Clinical isolates	*A. baumannii*
Hasan B et al 2014 [34]	2010-2011	Pakistan	Multicenter	Inpatients	ICU, medical and surgical wards of 3 healthcare facilities	Clinical isolates	*A. baumannii*
Mizutani T et al 2014 [2] (Japanese)	2004-2011	Japan	Multicenter	Unclear	14 Hospitals	Clinical isolates	*P. aeruginosa*
Nasrolahei M et al 2014 [35]	2013	Iran	Single center	Inpatients	Tertiary burn and ICU center	Clinical isolates	*A. baumannii*
Sader HS et al 2014 [36]	2011-2012	13 European countries + Israel + Turkey	Multicenter	Mixed	31 medical centers	Documented infections	Enterobacteriaceae *P. aeruginosa*
Siddaiahgari S et al 2014 [37]	2013	India	Single center	Inpatients	Pediatric oncology	Febrile neutropenia	Any
Farrell DJ et al 2013 [38]	2011-2012	USA	Multicenter	Inpatients	32 medical centers	Documented infections	Enterobacteriaceae *P. aeruginosa*

First Author-publication year	Study year/ period	Country	Single center/ multicenter	Outpatient / inpatient	Healthcare setting	Type of infection	Pathogens studied[1]
Japoni-Nejad A et al 2013 [39]	2011	India	Single center	Inpatients	Intensive care unit	Clinical isolates during an outbreak	*A. baumannii*
Galani I et al 2012 [40]	2008-2010	Greece	Multicenter	Unclear	4 tertiary hospitals	Clinical isolates	MDR *E. coli* *K. pneumoniae* *Enterobacter spp*
Jácome PR et al 2012 [41]	2006-2010	Brazil	Multicenter	Inpatients	5 teaching hospitals	Clinical isolates	*P.aeruginosa*
Gill M et al 2011 [42]	2010	Pakistan	Single center	Unclear	Military hospital	Clinical isolates	*P. aeruginosa*
Mahajan G et al 2011 [43]	2010-2011	India	Single center	Unclear	Tertiary hospital	Clinical isolates from urine, pus/wound swab, endotracheal secretions, sputum, body fluids, and blood	*A. baumannii*
Treviño M et al 2011 [44]	2009-2010	Spain	Single center	Inpatients	University hospital	Clinical isolates (including colonization)	imipenem-not-susceptible *Klebsiella* spp
Arroyo LA et al 2009 [45]	2000-2006	Spain	Single center	Unclear	Tertiary hospital	Clinical isolates	Colistin-resistant
Mukhopadhyay C et al 2008 [46]	2005-2007	India	Single center	Unclear	University hospital	Clinical isolates	*P. aeruginosa*

Abbreviations: CAUTI= catheter-associated urinary tract infection, CRBSI= catheter-related bloodstream infection, GNB= Gram-negative bacteria, ICU= intensive care unit, VAP= ventilator-associated pneumonia

[1]Data were extracted only for eligible pathogens based on our review criteria, i.e. PDR Gram-negative bacteria with susceptibility testing available for all the major antimicrobials (including carbapenems, polymyxins, aminoglycosides and tigecycline).

Supplementary Table 2; Studies reporting the outcome of and/or treatment regimens for PDR infections

First author-publication year	Study year/ period	Country	Design[1]	Healthcare setting	Type of infection	PDR pathogens [2]	Polymicrobial infections[3]	Data on treatment regimens
Alho AC et al 2019 [47]	Unclear	Portugal	Case report	ICU	BSI-osteomyelitis	*K. pneumoniae*	No	Yes
Assimakopoulos SF et al 2019 [48]	Unclear	Greece	Case-series (n=10)	ICU	VAP	*A. baumannii*	No	Yes
Parruti G et al 2019 [49]	2016-2017	Italy	Case report	Infectious Diseases Unit	BSI-osteomyelitis	*K. pneumoniae*	No	Yes
Abat et al 2018 [8][4]	2009-2015	France	Case series (n=2)	4 University hospitals	RTI	*B. cepacia*	Unclear	No
Agarwal S et al 2018 [50]	Unclear	India	Case series (n=2)	ICU	CRBSI, VAP	*C. indologenes*	Unclear	Yes
Cantón-Bulnes ML et al 2018 [51]	Unclear	Spain	Case report	Cystic fibrosis setting	RTI	*B. cepacia*	No	Yes
De Man TJB et al 2018 [52]	2016	USA	Case report	Hospital	Osteomyelitis	*K. pneumoniae*	No	Yes
Emre S et al 2018 [1] (Turkish)	Unclear	Turkey	Case series (n=2)	Prior ICU stay	STI, CRBSI	*K. pneumoniae*	Yes (1 of the 2 cases)	Yes
Katsiari M et al 2018 [14][4]	2011-2016	Greece	Case series (n=7)	ICU	BSI	*A. baumannii*	No	No
Molinaro M et al 2018 [53]	Unclear	Italy	Case report	ICU	Ventriculitis	*P. aeruginosa*	No	Yes

First author-publication year	Study year/ period	Country	Design[1]	Healthcare setting	Type of infection	PDR pathogens [2]	Polymicrobial infections[3]	Data on treatment regimens
Xiao J et al 2018 [18][4]	2006-2018	China	Case report (n=1 PDR)	Hospital	Meningitis	*A. baumannii*	No	Yes
Aires CAM et al 2017 [54]	2011	Brazil	Case report	Hospital	UTI	*K. pneumoniae*	No	No
Alvarez Lerma F et al 2017 [55]	2017	Spain	Case series (n=2)	ICU	VAP	*P. aeruginosa*	No	Yes
Sonnevend Á et al 2017 [56]	2014	United Arab Emirates	Case series (n=9)	Hospital	Clinical isolates	*K. pneumoniae*	Unclear	No
Souli M et al 2017 [57]	2012-2015	Greece	Case series (n=14)	2 Hospitals	Various sites	*K. pneumoniae*	Unclear	Yes
Xiong J et al 2017 [58]	2014	Canada	Case report	Hospital	RTI	*P. aeruginosa*	Unclear	No
Fernandes M et al 2016 [59]	2009-2013	India	Case series (n=2)	Ophthalmology	Keratitis	*P. aeruginosa*	No	Yes
Mandrawa et al 2016 [60]	Unclear	Australia	Case report	ICU	IAI	*K. pneumoniae*	No	Yes
Tsioutis C et l 2016 [29][4]	2012-2015	Greece	Case series	ICU	VAP	*A. baumannii*	Yes	No
Camargo JF et al 2015 [61]	Unclear	USA	Case report	ICU	BSI	*K. pneumoniae*	No	Yes
Douka E et al 2015 [62]	2011	Greece	Case series	ICU	BSI and UTI	*P. stuartii*	Unclear	Yes
Inchai J et al 2015 (two publications from the same cohort) [30, 31][4]	2005-2011	Thailand	Case series	ICU	VAP	*A. baumannii*	Yes	No

First author-publication year	Study year/ period	Country	Design[1]	Healthcare setting	Type of infection	PDR pathogens [2]	Polymicrobial infections[3]	Data on treatment regimens
Kulkova N et al 2015 [32][4]	2011-2012	Slovakia	Case report	Hospital	BSI	*P. aeruginosa*	Yes	Yes
Oliva A et al 2015 [63]	Unclear	Italy	Case report	Infectious Diseases	BSI	*K. pneumoniae*	No	Yes
Weterings V et al 2015 [64]	2013	Netherlands	Case series (n=2)	Hospital-nursing home	UTI	*K. pneumoniae*	No	No
Oliva A et al 2014 [65]	Unclear	Italy	Case series (n=3)	Hospital	BSI	*K. pneumoniae*	No	Yes
Treviño M et al 2011 [44][4]	2009-2010	Spain	Case report (n=1)	Hospital	BSI	*K. pneumoniae*	Unclear	Yes
Humphries RM et al 2010 [66]	2010	USA	Case report	ICU	CRBSI	*K. pneumoniae*	No	Yes
Layeux B et al 2010 [67]	Unclear	Belgium	Case series (n=2)	ICU	IAI, RTI	*P. aeruginosa*	Yes (1 of the 2 patients)	Yes
Elemam A et al 2009 [68]	2007-2008	USA	Case series (n=2)	Hospital	UTI, BSI	*K. pneumoniae*	No	Yes
Falagas ME et al 2008 [69]	2006-2007	Greece	Case series (n=2)	Hospital	RTI	*P. aeruginosa*	No	Yes
Mukhopadhyay C et al 2008 [46][4]	2005-2007	India	Case series (n=24)	Hospital	Not reported	*P. aeruginosa*	Unclear	Yes
Mentzelopoulos SD et al 2007 [70]	2005	Greece	Case series (n=5)	ICU	VAP	*P. aeruginosa*	Yes	Yes
Beno P et al 2006 [71]	2004-2005	Slovakia	Case series (n=7)	ICU	BSI	*P. aeruginosa*	Yes (6 of the 7 patients)	No

First author-publication year	Study year/ period	Country	Design[1]	Healthcare setting	Type of infection	PDR pathogens [2]	Polymicrobial infections[3]	Data on treatment regimens
Falagas ME et al 2005 [72]	2003-2004	Greece	Case series (n=5)	ICU	RTI, UTI, BSI	*P. aeruginosa*	Unclear	Yes

Abbreviations: BSI= bloodstream infection, CAUTI= catheter-associated urinary tract infection, CRBSI= catheter-related bloodstream infection, GNB= Gram-negative bacteria, IAI= intra-abdominal infection, ICU= intensive care unit, STI= soft tissue infection, VAP= ventilator-associated pneumonia

[1] Design regarding the analysis of outcomes and treatment regimens of PDR infections.

[2] Data were extracted only for eligible pathogens based on our review criteria, i.e. PDR Gram-negative bacteria with susceptibility testing available for all the major antimicrobials (including carbapenems, polymyxins, aminoglycosides and tigecycline).

[3] Including patients with infection by other pathogen at another site.

[4] Also in Supplementary Table 1A

Supplementary Table 3; Studies reporting PDR isolates but without information regarding the proportion of pandrug resistance, treatment or outcome[1]

Author-date	Study period/ year	Country	Healthcare setting	Type of infection	PDR isolates
Finklea et al 2018 [73]	2015	USA	Cystic fibrosis clinic	Respiratory samples	*P. aeruginosa*
Leite GC et al 2016 [74]	Unclear	Brazil	Microbiology laboratory	Clinical isolates	*A. baumannii*
Cassu-Corsi D et al 2015 [75]	2013	Brazil	Hospital	Urinary isolates	*K. pneumoniae*
Gruber TM et al 2015 [76]	2014	Germany	Hospital	Colonization, UTI	*S. marcescens*
Zowawi HM et al 2015 [77]	2014	United Arab Emirates	Hospital	Urinary isolate	*K. pneumoniae*
Göttig S et al 2014 [78]	2013	Germany	ICU	Colonization	*A. baumannii*
Tsioutis C et al 2010 [79]	2006-2008	Greece	Hospital	Variable	*A. baumannii*
Lepsanovic Z et al 2008 [80]	2004-2007	Serbia	Hospital	Clinical isolates	*P. aeruginosa*

Author-date	Study period/ year	Country	Healthcare setting	Type of infection	PDR isolates
Hsueh PR et al 2005 [81]	1999-2002	Taiwan	Hospital	Infection/colonization	*P. aeruginosa*
Dobbin C et al 2004 [82]	1989-2002	Australia	Cystic fibrosis center	Isolates from sputum of pre-transplant patients with cystic fibrosis	*P. aeruginosa*

[1] These studies were included for epidemiological purposes (geographical distribution of PDR, types of PDR isolates, source of PDR isolates).

Supplementary Table 4; Commonly missing (susceptibility testing not performed or not reported[1]) antimicrobials in studies reporting pandrug-resistant Gram-negative bacteria

	Number (%) of studies in which susceptibility testing was missing or not reported[1]			Number (%) of PDR isolates for which susceptibility testing was missing or not reported[1]		
	Enterobacteriaceae (n=33 studies)	Pseudomonas (n=33 studies)	Acinetobacter (n=19)	Enterobacteriaceae (n=163)	Pseudomonas (n=175)	Acinetobacter (n=172)
Fosfomycin	13 (39%)	25 (78%)[2]	Intrinsic resistance[3]	64 (39%)	163 (93%)[2]	Intrinsic resistance[3]
Trimethoprim/ sulfamethoxazole	6 (18%)	Intrinsic resistance[3]	7 (37%)	19 (12%)	Intrinsic resistance[3]	102 (59%)
Ampicillin/sulbactam[4]	Not applicable[5]	Not applicable[5]	5 (26%)	Not applicable[5]	Not applicable[5]	111 (65%)
Minocycline	25 (78%)	Intrinsic resistance[3]	15 (79%)	121 (74%)	Intrinsic resistance[3]	145 (84%)
Amikacin	5 (15%)	4 (12%)	3 (16%)	29 (18%)	13 (7%)	15 (9%)
Gentamicin	0	8 (24%)	2 (11%)	0	58 (33%)	19 (11%)

[1] It is possible than in some of the studies susceptibility testing was performed but not reported for some of these antibiotics

[2] Breakpoints for *P. aeruginosa* for intravenous fosfomycin have not been established and there are concerns about the in vivo activity of fosfomycin against *P. aeruginosa* (even when susceptible in vitro) and the risk of emergence of resistance during treatment [83]

[3] According to EUCAST expert rules

[4] Or cefoperazone/sulbactam

[5] Resistance can be inferred based on resistance to more broad-spectrum agents (e.g. carbapenems)

Supplementary Table 5; Non-eligible studies due to missing susceptibility testing for major antimicrobial groups

First author- Year of publication	Country	Missing antimicrobial groups	Number of possible PDR isolates[#]
Čiginskienė A et al 2019 [84]	Lithuania	polymyxins	11
Los-Arcos I et al 2019 [85]	Spain	carbapenems, tetracyclines and trimethoprim-sulfamethoxazole	13
Varsha M et al 2019 [86]	USA	tigecycline	7
Aljanaby AAJ et al 2018 [87]	Iraq	carbapenems, polymyxins, tigecycline	9
Aljanaby AAJ et al 2018 [88]	India	polymyxins, tigecycline	19
Bickenbach J et al 2018 [89]	Germany	polymyxins	
Demoz GT et al 2018 [90]	Ethiopia	polymyxins, tigecycline	1
El-Shouny et al 2018 [91]	Egypt	polymyxins	20
Gao Q et al 2018 [92] (Chinese) *	China	polymyxins	
Gashaw et al 2018 [93]	Ethiopia	polymyxins, tigecycline	24
Guducuoglu et al 2018 [94]	Turkey	tigecycline	8
Nuryastuti T et al 2018 [95]	Indonesia	tigecycline	1
Sağmak-Tartar A et al 2018 [96] (Turkish)*	Turkey	tetracyclines, tigecycline	
Shrestha D et al 2018 [97]	Nepal	polymyxins, tigecycline	1
Wu HG et al 2018 [98]	China	polymyxins	42
Xu T et al 2018 [99] (Chinese)*	China	polymyxins, tigecycline	
Gonçalves GB et al 2017 [100]	Brazil	polymyxins, tigecycline	3
Jing C, Wang C 2017 [101] (Chinese) *	China	polymyxins, tigecycline	
Nowak J et al 2017 [102]	Europe	tigecycline	20
Reale M et al 2017 [103]	Italy	aminoglycosides	27
Samad A et al 2017 [104]	Pakistan	polymyxins	3
Swe Swe-Han K et al 2017 [105]	South Africa	tetracyclines, tigecycline	7
Uzoamaka M et al 2017 [106]	Nigeria	polymyxins, tigecycline	
Kryzhanovskaya OA et al 2016 [107]	Russia	tigecycline	2

First author- Year of publication	Country	Missing antimicrobial groups	Number of possible PDR isolates[#]
(Russian) *			
Li X et al 2016 [108]	China	polymyxins, tigecycline	27
Lolans K et al 2005 [109]	USA	polymyxins	1
Ren G et al 2016 [110]	China	polymyxins, tigecycline	
Zhang Y et al 2016 [111] (Chinese)*	China	polymyxins	921
Chen Y et al 2015 [112] (Chinese)*	China	polymyxins	81
Guo X et al 2015 [113] (Chinese)*	China	tigecycline	
He L et al 2015 [114] (Chinese)*	China	polymyxins, tigecycline	
Hu F et al 2015 [115] (Chinese)*	China	polymyxins, tigecycline	
Kim Y et al 2015 [116]	South Korea	tetracyclines, tigecycline	1
Lobo LJ et al 2015 [117]	USA	polymyxins, tigecycline	14
Murugan N et al 2015 [118]	India	polymyxins	
Pei HH et al 2015 [119] (Chinese)*	China	polymyxins, tigecycline	
Qiang X et al 2015 [120] (Chinese)*	China	polymyxins, tigecycline	
Qin H et al 2015 [121] (Chinese)*	China	polymyxins, tigecycline	63
Shao C et al 2015 [122] (Chinese)*	China	polymyxins, tigecycline	
Shapoval SD et 2015 [123] (Russian)*	Ukrain	polymyxins	13
Tian L et al 2015 [124] (Chinese)*	China	polymyxins, tigecycline	
Anvarinejad M et al 2014 [125]	Iran	polymyxins	35
Han X et al 2014 [126]	China	polymyxins, tigecycline	6
Han X et al 2014 [127] (Chinese) *	China	polymyxins, tigecycline	6
Hong-Li Tan et al 2014 [128]	China	polymyxins	1
Li-wan W et al 2014 [129] (Chinese)*	China	tigecycline	42
Moroh JLA et al 2014 [130]	Cote d'Ivoire	carbapenems, tigecycline	70
Rajkumari N et al 2014 [131]	India	polymyxins	847
Ranjan S et al 2014 [132]	India	polymyxins	7
Reddy R et al 2014 [133]	India	tetracyclines, tigecycline	4

First author- Year of publication	Country	Missing antimicrobial groups	Number of possible PDR isolates[#]
Shen Z et al 2014 [134] (Chinese)*	China	polymyxins, tigecycline	
Singh et al 2014 [135]	India	tetracyclines, tigecycline	18
Viswanathan R et al 2014 [136]	India	polymyxins, tigecycline	5
Garbati MA et al 2013 [137]	Saudi Arabia	polymyxins	1
Liu Y et al 2013 [138] (Chinese)*	China	polymyxins, tigecycline	12
Movahedi Z et al 2013 [139]	Iran	polymyxins	11
Shi H et al 2013 [140] (Chinese)*	China	polymyxins	108
Shi W et al 2013 [141]	China	polymyxins, tigecycline	5
Sivaranjani V et al 2013 [142]	India	polymyxins	15
Wang Q et al 2013 [143]	China	polymyxins, tigecycline	3
Yang J et al 2013 [144] (Chinese)*	China	polymyxins	20
Zhang H et al 2013 [145] (Chinese)*	China	polymyxins, tigecycline	1635
Zhang Y et al 2013 [146]	China	tigecycline	25
Zhu D et al 2013 [147] (Chinese)*	China	polymyxins, tigecycline	860
Zhu R et al 2013 [148] (Chinese)*	China	polymyxins, tigecycline	119
Arduino SM et al 2012 [149]	Argentina	tetracyclines, tigecycline	5
Chen Z et al 2012 [150] (Chinese)*	China	polymyxins, tigecycline	8
Li B et al 2012 [151]	China	polymyxins, tigecycline	4
Manageiro V et al 2012 [152]	Portugal	polymyxins	
Park HJ et al 2012 [153]	South Korea	polymyxins, tigecycline	234
Xu J et al 2012 [154]	China	polymyxins, tigecycline	
Yong-Qiang H et al 2012 [155] (Chinese)*	China	polymyxins, tigecycline	
Zhang Y et al 2012 [156] (Chinese*)	China	polymyxins	86
Zhu D et al 2012 [157] (Chinese)*	China	polymyxins, tigecycline	
Zhuo C et al 2012 [158] (Chinese)*	China	polymyxins, tigecycline	223
Babu KVY et al 2011 [159]	India	polymyxins, tigecycline	35
Ben RJ et al 2011 [160]	Taiwan	polymyxins, tigecycline	

First author- Year of publication	Country	Missing antimicrobial groups	Number of possible PDR isolates[#]
Chen Z et al 2011 [161]	China	tigecycline	
Huiming X et al 2011 [162] (Chinese)*	China	polymyxins, tigecycline	1058
Li H et al 2011 [163] (Chinese)*	China	polymyxins, tigecycline	
Su D et al [164] (Chinese)*	China	polymyxins, tigecycline	
Zhu D et al 2011 [165] (Chinese)*	China	polymyxins, tigecycline	1037
Jian C et al 2010 [166] (Chinese)*	China	polymyxins, tigecycline	188
Joung MK et al 2010 [167]	South Korea	polymyxins, tigecycline	18
Pang XL et al 2010 [168] (Chinese)*	China	polymyxins	8
Sengstock DM et al 2010 [169]	USA	polymyxins, tigecycline	56
Wang F et al 2010 [170] (Chinese)*	China	polymyxins, tigecycline	882
Zhang X et al 2010 [171] (Chinese)*	China	polymyxins, tigecycline	709
Zhang Y et al 2010 [172] (Chinsese)*	China	polymyxins	84
Zhu D et al 2010 [173] (Chinese)*	China	polymyxins, tigecycline	634
Zhuo C et al 2010 [174]	China	polymyxins, tigecycline	111
Chuang YY et al 2009 [175]	Taiwan	polymyxins, tigecycline	11
Sun J et al 2009 [176] (Chinese)*	China	polymyxins	128
Taherikalani M et al 2009 [177]	Iran	aminoglycosides	7
Taşbakan MS et al 2009 [178] (Turkish)*	Turkey	polymyxins, tigecycline	9
Valencia R et al 2009 [179]	Spain	tigecycline	12
Wang F et al 2009[180] (Chinese)*	China	polymyxins, tigecycline	453
Xiao SC et al 2009 [181]	China	aminoglycosides, tigecycline	1
Zhu DM et al 2009 [182] (Chinese)*	China	polymyxins, tigecycline	251
Zhu J et al 2009 [183]	China	polymyxins, tigecycline	1
Vonberg RP et al 2008 [184]	Germany	aminoglycosides, polymyxins, tigecycline	12
Wang F et al 2008 [185] (Chinese)*	China	polymyxins, tigecycline	543
Zhu DM et al 2008 [186] (Chinese)*	China	polymyxins, tigecycline	219
Chan PC et al 2007 [187]	Taiwan	polymyxins, tigecycline	9

First author- Year of publication	Country	Missing antimicrobial groups	Number of possible PDR isolates[#]
Hadjiliadis D et al 2007 [188]	USA	polymyxins	45
Huang SS et al 2007 [189]	Taiwan	aminoglycosides, polymyxins, tigecycline	22
Ni YX 2007 [190] (Chinese)*	China	polymyxins	98
Shi Y et al 2007 [191] (Chinese)*	China	polymyxins, tetracyclines, tigecycline	77
Sun JY and Ni YX 2007 [192] (Chinese)*	China	polymyxins, tigecycline	656
Zhu DM et al 2007 [193] (Chinese)	China	polymyxins, tigecycline	158
Zhuo C et al 2007 [194] (Chinese)*	China	polymyxins, tigecycline	6
Lee K et al 2006 [195]	South Korea	polymyxins, tigecycline	318
Lim YM et al 2006 [196] (Korean)*	South Korea	tetracyclines, tigecycline	12
Vahaboglu H et al 2006 [197]	Turkey	polymyxins	9
Vonberg RP et al 2006 [198]	Germany	polymyxins, tetracyclines	53
Wang F 2006 [199] (Chinese)	China	polymyxins, tigecycline	264
Zhu DM et al 2006 [200] (Chinese)*	China	polymyxins, tigecycline	242
Chen SF et al 2005 [201]	Taiwan	aminoglycosides, polymyxins, tigecycline	1
Lee CM et al 2005 [202]	Taiwan	aminoglycosides, polymyxins, tigecycline	89
Tian BW et al 2005 [203] (Chinese) *	China	polymyxins	18
Vonberg RP et al [204] (German)*	Germany	polymyxins, tetracyclines, aminoglycosides, tigecycline	108
Kuo LC et al 2004 [205]	Taiwan	polymyxins, tigecycline	15
Marais E et al 2004 [206]	South Africa	polymyxins, tigecycline	
Hsueh PR et al 2002 [207]	Taiwan	polymyxins, tigecycline	203
Malik F et al 2012 [208]	Pakistan	polymyxins, tigecycline	29
Tsiodras S et al 2000 [209]	USA	polymyxins, tigecycline	21

* Articles evaluated using Google Translate.

[#] May include duplicates. In some studies, the exact number of PDR isolates was not reported.

Supplementary Table 6; Non-eligible studies due to lack of reporting of the list of antimicrobial agents tested

First author- Year of publication	Country	Number of possible PDR isolates
Attia H et al 2019 [210]	Egypt	2
Perdigão Neto et al 2019 [211]	Brazil	13
Del Prete R et al 2019 [212]	Italy	33
Lay C et al 2019 [213]	USA	697
Chen X et al 2018 [214]	China	4
Moodley K et al 2018 [215]	South Africa	7
Guo Y et al 2017 [216]	China	10
Kimura N et al 2016 [217]	USA	508
Bhatt P et al 2015 [218]	India	11
Dimopoulos G et al 2015 [219]	Greece	4
Li M et al 2015 [220] (Chinese)*	China	110
Merli M et al 2015 [221]	Italy	2
Tuon FF et al 2015 [222]	Brazil	5
Mazi W et al 2014 [223]	Saudi Arabia	1
Savi D et al 2014 [224]	Italy	1
Chen H et al 2013 [225] (Chinese)*	China	53
Mai M et al 2013 [226] (Chinese)*	China	61
Digoy GP et al 2012 [227]	USA	2
Özkurt Z et ak 2012 [228]	Tuerky	
Tabah A et al 2012 [229]	Europe	3
Ran YC et al 2010 [230]	China	6
Apisarnthanarak A et al 2009 [231]	Thailand	
LiPuma JJ et al 2009 [232]	USA	20
Tao C et al 2009 [233]	China	16
Lin GM et al 2008 [234]	Taiwan	1
Egan TM et al 1998 [235]	USA	36

Supplementary Table 7; Non-eligible studies using the term pandrug resistance (or pan-resistant) for isolates susceptible to at least one antibiotic

Kanjanawasri S et al 2018 [236]	PDR isolates were resistant "to all antibiotic groups except tigecycline and colistin"
Owrang M et al 2018 [237]	"All of the isolates were pandrug resistant A. baumannii and the lowest resistance rates were observed toward minocycline and amikacin (93.33% in both) and trimethoprim/sulfamethoxazole (92.38%)."
Rebic V et al 2018 [238]	Polymyxin not tested in most isolates. All isolates with susceptibility testing to colistin available were susceptible.
Siddiqui AH et al 2018 [239]	PDR definition: "Bacteria resistant to almost all classes of antibiotics including polymyxins"
Yi ML et al 2018 [240]	All isolates were susceptible to tigecycline
Alipour N et al 2017 [241]	Colistin-resistant Pseudomonas aeruginosa isolates that were all susceptible to alternative antibiotics
Pan A et al 2017 [242]	All isolates described as PDR were susceptible to collistin
Chen H et al 2016 [243] (Chinese)*	Case report. *K. pneumonieae*. Susceptible to tigecycline and the patient responded to treatment with tigecycline.
Li J et al 2016 [244] (Chinese)*	n=3 bla_{NDM-1} K. pneumoniae isolates. All were susceptible to amikacin and polymyxin B.
Mohamed YF et al 2016 [245]	"The four bacterial isolates used in this study were confirmed to be pan-drug resistant by the antibiotic susceptibility testing being resistant to all antibiotic classes except colistin "
Singh SK, Gupta M 2016 [246]	Carbapenem-resistant-colistin-resistant *Klebsiella pneumoniae* susceptible to tigecycline and cotrimoxazole
Vourli S et al 2015 [247]	*A. baumannii*. "Tigecycline MICs ranged from 0.5 mg/L to 1 mg/L"
Zhi-Wen Y et al 2015 [248]	The PDR term was used for XDR bacteria
Iraz M et al 2014 [249]	*Pseudomonas aeruginosa* susceptible to colistin
Ning F et al 2014 [250]	*Acinetobacter baumannii* susceptible to polymyxin
Dash M et al 2013 [251]	All 8 PDR isolates were susceptible to colistin
Friedstat JS et al 2013 [252]	"Pan-resistance" is reported in 15 patients, however "only one instance of colistin resistance was identified". The list of agents tested to evaluate for pan-resistance is not reported.
Liu L et al 2013 [253] (Chinese)	All isolates were sensitive to amikacin
Qi M et al 2013 [254]	Case report of A. baumannii successfully treated with tigecycline (pan-resistant to other options)

Shao BB, Feng HB 2013 [255]	Case report of A. baumannii successfully treated with tigecycline (pan-resistant to other options)
Sun CD et al 2013 [256] (Chinese)	"sensitive rate was 100% to polymyxin"
Borcan E et ak 2012 [257]	**"**PDR respresents resistance to all antibiotics, except colistin." All isolates were susceptible to colistin
Simsek F et al 2012 [258]	Case report. P. aeruginosa susceptible to polymyxin B
Zhang Z et al 2012 [259]	PDR is used to refer to carbapenem-resistant strains.
Prata-Rocha ML et al 2012 [260]	"An isolate was deemed pan-resistant if it was resistant to all commonly tested antibiotics except colistin"
Kim YJ et al 2011 [261]	All PDR *Acinetobocter baumannii* were susceptible to colistin
Ning FG et al 2011 [262]	PDR *P. aeruginosa* isolates were "resistant to all available antibiotics, including third-generation cephalosporin, carbapenems and ciprofloxacin, but not polymyxin". Unclear if susceptibility testing for aminoglycosides was performed.
Ozdem B et al 2011 [263] (Turkish)	*A. baumannii*. All isolates were susceptible to tigecycline. Polymyxin testing was not performed.
Rodrigues AC et al 2011 [264]	All samples of "pan-resistant" *P. aeruginosa* were sensitive in vitro to polymyxin B.
Saleem AF et al 2011 [265]	All PDR *Acinetobocter baumannii* were susceptible to polymyxin
Salomon J et al 2011 [266]	Case report. "*P. aeruginosa* susceptible only to colimycin". "*A. baumanii* susceptible only to colimycin". "*K. pneumoniae* had a phenotypic resistance against almost all relevant antimicrobial agents except for colistin".
Sun Z et al 2011 [267] (Chinese)*	"There were obvious difference among the drug-resistance rates of AB strains to 13 antibiotics (with rates from 42.31% to 100.00%)" i.e. susceptibility to at least one antibiotic was 100%
Tekçe AY et al 2011 [268]	Case report of a "pan-resistant" *A. baumannii*, susceptible to colistin and tigecycline. The patients was successfully treated with tigecycline.
Telang NV et al 2011 [269]	Case report. "The isolate was only susceptible (moderately) to colistin." Tigecycline was not tested.
Zhao WS et al 2011 [270]	Case report of "pandrug"-resistant *Acinetobacter baumannii* bacteremia. Susceptibility to tigecycline and polymyxins is not reported. The patient was successfully treated with tigecycline.
Glupczynski Y et al 2010 [271]	"Fifteen of the isolates were found to co-produce ESBLs and VIM carbapenemases. These strains were pan-resistant and remained susceptible only to colistin (MICs <or= 2 mg/L)"
Huang J et al 2010 [272]	All PDR isolates were susceptible colistin
Sun SM et al 2010 [273] (Chinese)	Case series of 9 patients with infections by "pan-drug" resistant *Acinetobacter baumannii*. "The polymyxin sensitivity were 100% for these infections"
Werarak P et al 2010 [274]	"PDR is defined as resistance to all classes of anti-pseudomonas antibiotics except polymyxins"
Apisarnthanarak A et al 2009 [275]	PDR defined as "resistant to all antibiotic classes except colistin". + tigecycline was not evaluated

Saleem AF et al 2009 [276]	"Pan-resistance (87/122; sensitive only to Polymyxin) was present in 71% of Acinetobacter isolates."
Apisarnthanarak A 2008 and 2009 [277, 278]	PDR *A. baumannii* was defined as an *A. baumannii* isolate that was resistant to all currently available systemic antibiotics, including cephalosporins, aztreonam, carbapenems, aminoglycosides, fluoroquinolones, and sulbactam (except polymyxin B)
Arikan Akan O, Uysal S 2008 [279] (Turkish)*	All *K. pneumoniae* isolates were susceptible to tigecycline. 5 of 100 carbapenem-resistant *A.baumannii* were non-susceptible (MIC=3) to tigecycline but concurrent susceptibility to other agents (e.g. colistin) is not reported.
Pinheiro MR et al 2008 [280]	PDR defined as resistance to all antibiotics except polymyxin
Pitout JD et al 2008 [281]	"No colistin resistance was detected"
Doi Y et al 2007 [282]	The PDR isolate was susceptible to colistin
Fica C A et al 2007 [283] (Spanish)*	PDR defined as resistant to 3rd generation cephalosporins, quinolones, aminoglycosides and carbapenems. Only 1 isolate was non-susceptible to colistin. Tigecycline was not evaluated
Goverman J et al 2007 [284]	Pan-resistance was defined based on susceptibility to the following antibiotics: amikacin, gentamicin, tobramycin, ceftazidime, meropenem, piperacillin, ticarcillin, and ciprofloxacin. All patients with PDR bacteria were treated with colistin.
Jayakumar S, Appalaraju B. 2007 [285]	"All of the strains were sensitive to polymyxin"
Kallel H et al 2007 [286]	"In all patients in this group, A. baumanii and P. aeruginosa were PDR and were susceptible only to colistin"
Naas T et al 2007 [287]	The PDR isolate was susceptible to colistin
Peña C et al 2007 [288]	All isolates were uniformly susceptible to colistin
Taccone FS et al 2006 [289]	The PDR A. baumannii isolate was susceptible to both colistin and tigecycline
Wang CY et al 2006 [290]	All isolates were susceptible to colistin
Wang H et al 2006 [291] (Chinese)*	All PDR were susceptible to minocycline and colistin
Deplano A et al 2005	All isolates were susceptible to colistin
Miriagou V et al 2005 [292]	All isolates were susceptible to colistin
Wang SH et al 2003 [293]	Isolates were susceptible to polymyxin B
Demko CA et al 1998 [294]	Panresistant was defined as "susceptible to no more than one antimicrobial agent". + the list f agents tested is not reported

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