Clinical Infectious Diseases

STATE OF THE ART REVIEW

State of the Management of Infections Caused by Multidrug-Resistant Gram-Negative Organisms

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In the past decade, the prevalence of multidrug-resistant gram-negative (MDR-GN) bacterial infections has increased significantly, leading to higher rates of morbidity and mortality. Treating these infections poses numerous challenges, particularly when selecting appropriate empiric therapy for critically ill patients for whom the margin for error is low. Fortunately, the availability of new therapies has improved the treatment landscape, offering safer and more effective options. However, there remains a need to establish and implement optimal clinical and therapeutic approaches for managing these infections. Here, we review strategies for identifying patients at risk for MDR-GN infections, propose a framework for the choice of empiric and definitive treatment, and explore effective multidisciplinary approaches to managing patients in the hospital while ensuring a safe transition to outpatient settings.

Keywords. multidrug resistance; gram-negative.

In the United States, an estimated 2 868 700 infections are caused by resistant bacteria and fungi annually, with 35 900 related deaths, including several antibiotic-resistant gram-negative (GN) bacteria that are identified by the Centers for Disease Control and Prevention as national threats [1]. Multidrug-resistant gram-negative (MDR-GN) organisms, defined as organisms nonsusceptible to ≥1 agent in ≥3 antimicrobial categories [2], pose serious management challenges. Preemptively identifying patients with MDR-GN infections is challenging and is associated with increased morbidity and mortality [3,4]. Therefore, ensuring appropriate and effective antimicrobial therapy, defined as in vitro susceptibility of the infection pathogen to prescribed antibiotics, is important [5]. This is particularly impactful in septic patients [6–9]. The importance of timing of effective empiric therapy was demonstrated in a subpopulation of 2 154 septic patients with shock, where each hour delay in antibiotic administration from the time of hypotension onset was associated with a mean decrease in survival of 7.6% [6]. To evaluate the impact of empiric ineffective antimicrobial therapy, one study included 789 patients with GN bacteremia and showed that patients who received ineffective empiric antibiotics had a higher risk of 30-day all-cause mortality (hazard ratio, 1.68; 95% confidence interval, 1.19–2.38) [7]. Importantly, the likelihood of empiric therapy being ineffective increases with the degree and breadth of antimicrobial resistance of the pathogen. For example, one study reported that patients with carbapenem-resistant *Enterobacteriaceae* (CRE) infection were 3 times more likely to receive ineffective therapy than non-CRE patients, resulting in increased mortality, length of stay, and cost [4].

Although newer therapies for MDR-GN infections are available [10], resistance has already emerged [11]. Stratifying the risk of MDR-GN infection prior to starting empiric treatment increases the likelihood that effective therapy is delivered to patients who have MDR-GN infections while limiting unnecessary use of broad and novel agents in patients with a lower likelihood of such infections and thus reduces the risk for emergence of resistance [11].

Management of MDR-GN infections is multifaceted and includes knowledge of national and local antimicrobial resistance epidemiology and optimal treatment options, interpretation of rapid diagnostic testing (RDT) platforms (when available), de-escalation to definitive therapy after diagnosis is confirmed, and effective transition of care to nonhospital settings [12].

A multidisciplinary approach improves the likelihood of providing effective and safe care and often includes the primary care team, infectious diseases (ID) consultants, antimicrobial stewardship (AS) pharmacists or personnel, unit-specific

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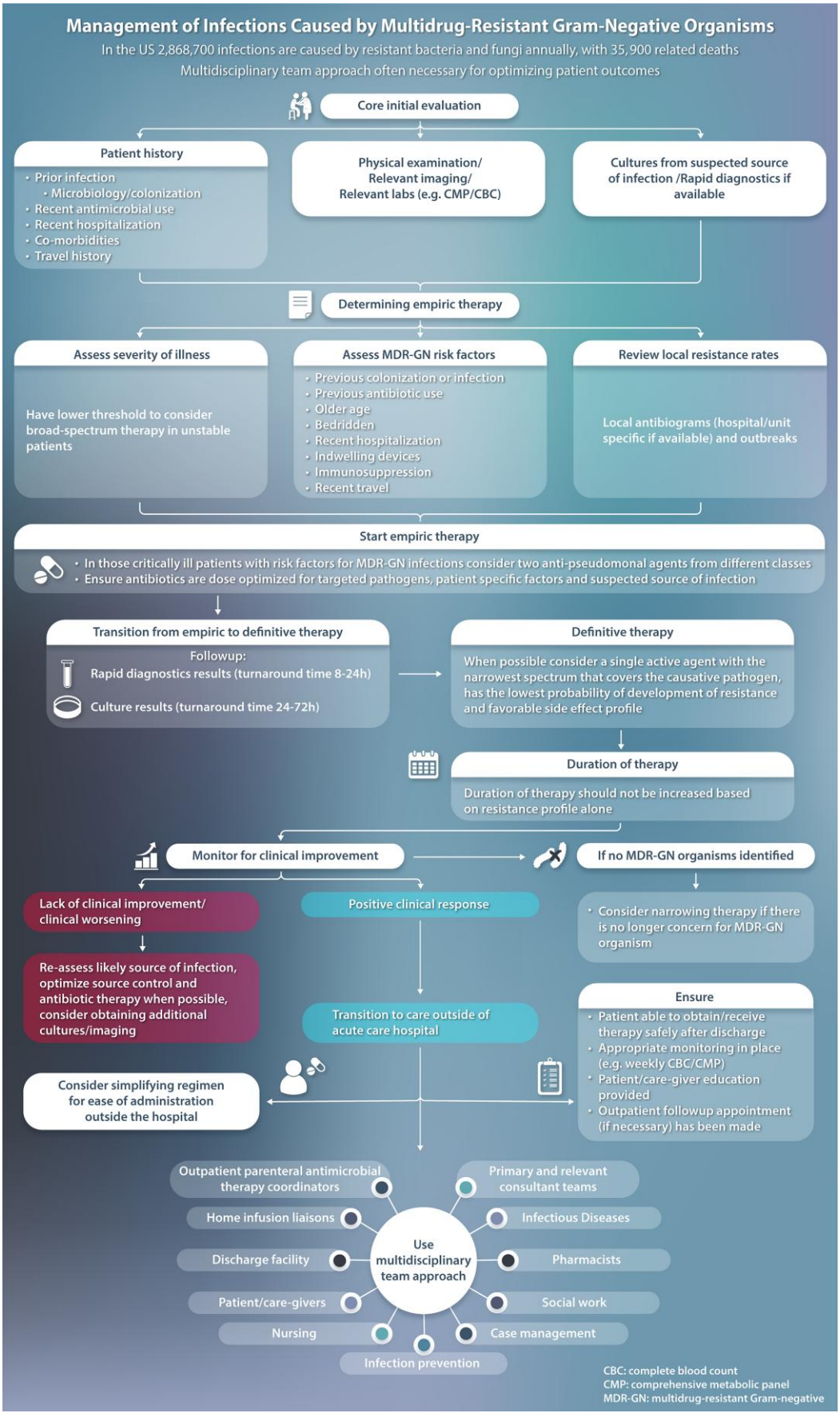


pharmacists, clinical microbiology, infection prevention, critical care teams, additional relevant specialists, nurses, and patients and/or caregiver(s). Upon discharge, this group may additionally include case managers, social workers, outpatient parenteral antimicrobial therapy (OPAT) coordinators, home infusion liaisons, discharge facility and patient educators.

In this review, we discuss risk factors for MDR-GN infections, how to effectively choose empiric and definitive treatment, relevant monitoring parameters for treatment response, and important factors related to safe transition of care upon patient discharge.

PATIENT CASE

An 82-year-old female was transferred from a nursing home to the emergency department (ED) due to hypotension and fevers. The patient had been experiencing coughing and pleuritic chest pain for 1 week before presentation and was treated with piperacillin-tazobactam at the nursing home for 5 days without improvement in symptoms. The patient has a history of hypertension, diabetes mellitus, and chronic kidney disease. Approximately 2 months prior, the patient was hospitalized and underwent embolization for a ruptured cerebral aneurysm. The patient was admitted to the intensive care unit (ICU) for 10 days, remained in the hospital for 18 days, was treated for a ceftriaxone-resistant *Escherichia coli* urinary tract infection (UTI) with 7 days of piperacillin-tazobactam, and then was discharged to the nursing home. One month prior to presentation, the patient was again treated for a UTI with 7 days of levofloxacin.

On initial examination in the ED, the patient was dyspneic with blood pressure of 80/42 mm Hg, pulse at 120 beats per minute, temperature of 101.2 °F, respiratory rate of 28 breaths per minute, and oxygen saturation of 86% on room air. There were crackles at the left lung base. Laboratory test results showed a white blood cell count (WBC) of $18 \times 10^3/\mu L$ (baseline $6 \times 10^3/\mu L$), neutrophils of 96.9%, lactate of 4 mmol/L, and serum creatinine of 3 mg/dL (baseline 1.5 mg/dL). A chest radiograph revealed a dense infiltrate on the left side. The patient's respiratory status deteriorated quickly in the ED. The patient was intubated and started on norepinephrine. Two sets of blood cultures and respiratory cultures were obtained.

Which GN antimicrobial should be empirically started?

APPROACH TO EMPIRIC THERAPY AND DIAGNOSTIC WORKUP

When determining the appropriate empiric regimen, it is crucial to consider the likely source of infection, the potential pathogens involved, and the potential consequences if initial antibiotics prove ineffective (ie, the patient's level of acuity and instability) [13].

Diagnostic Workup

The diagnostic workup for MDR-GN infection follows an approach that is similar to the workup for any other type of infection but with an emphasis on obtaining a comprehensive patient history that includes previous infections, healthcare exposure, travel history, culture results, and antibiotic usage, as well as conducting routine diagnostic evaluations [13]. The use of available RDT can facilitate more rapid pathogen identification [5, 14, 15].

Risk Factors for MDR-GN Infections

Optimizing empiric therapy for MDR-GN infections includes assessing the risk for such pathogens [5, 16]. The selection of an appropriate empiric agent should consider local epidemiology, patient risk factors/profile for resistant pathogens, site of infection, disease severity, and the potential consequences of ineffective empiric therapy, including the risk of mortality [5, 14, 15].

Prevalence of MDR-GN pathogens vary locally, globally, and even within different wards of a hospital [17, 18]. Patient location at the time of symptom onset (community, long-term care, hospital) is important in evaluating the likelihood of MDR pathogens [15, 18, 19]. Local antibiograms, including unit-based and/or syndromic antibiograms (which incorporate the weighted incidence of pathogens causing the syndrome), should be used when available to guide empiric therapy [17, 19, 20]. However, it is important to note that these antibiograms may be outdated or may not include susceptibility rates of newer antimicrobials. This is particularly relevant in institutions that experience high rates of MDR-GN infections. Awareness of the predominant local organisms of concern and recent outbreaks is crucial, especially in areas with outdated antibiograms.

The most commonly cited risk factors for MDR-GN pathogens include antibiotic exposure in the prior 30 days and infection or colonization with MDR-GN pathogens in the prior 6 months [5]. Some experts recommend covering for MDR-GN pathogens empirically if the hospital prevalence shows more than 20% resistance to a potential empiric agent (eg, if local epidemiology data indicate a prevalence of more than 20% cefepime-resistant *Enterobacterales*, instead of initiating cefepime empirically for a critically ill patient, consider meropenem) [12, 14]. Additional risk factors to consider include older age, advanced comorbidities (eg, immunosuppression, bedridden status), prolonged or recent hospitalization (within the last 12 months), use of indwelling devices, and travel history to regions with high MDR-GN prevalence [5, 14, 15]. International travel has been identified as a contributor to the spread of resistance, with varying rates of resistance observed in different countries. For example, the prevalence of New Delhi metallo-β-lactamase–producing *E. coli* was found to be 82.6%, 12.9%, 1.5%, 1.0%, and 2.0% in Asia, Europe, North America, Africa,

and Oceania, respectively [21]. A meta-analysis showed the highest carriage rates of MDR *Enterobacterales* were observed after travel to southern Asia (median 71%), followed by travel to northern Africa (median 42%) [22]. Multiple predictive models have been published on MDR-GN infection identification with varying risk factors [23–33]. The most optimal and generalizable predictive model for MDR-GN is not known [34]. Moreover, therapeutic challenges may arise due to overlapping risk factors for different types of MDR-GN pathogens, as novel agents exhibit varying activity against different MDR-GN pathogens.

In severe infectious syndromes where consequences of delayed institution of effective therapy can be catastrophic, considerations for empiric coverage for MDR-GNR pathogens are particularly important. In patients with even a small risk for an MDR-GN pathogen, initial antimicrobial therapy should be prompt and cover all pathogens with a reasonable likelihood of being present [6–9, 16]. However, for hemodynamically stable patients and/or those with less severe infections (eg, a stable patient with a diabetic foot infection), a more targeted empiric regimen based on local epidemiology, which may not provide extensive coverage for MDR-GN, is reasonable [15, 35].

Approach to Early Empiric Therapy

When considering an empiric antibiotic treatment to provide coverage against relevant MDR-GN pathogens, we suggest a multifactorial approach, taking the local epidemiology of MDR-GN pathogens, patient risk factors, and acute severity of illness into account (see Figure 1).

In most US hospitals, the incidence of difficult-to-treat, resistant *Pseudomonas aeruginosa* (DTRP; *P. aeruginosa* that exhibits nonsusceptibility to all of the following: piperacillin-tazobactam, ceftazidime, cefepime, aztreonam, meropenem, imipenem-cilastatin, ciprofloxacin, and levofloxacin), CRE, and carbapenem-resistant *Acinetobacter baumannii* (CRAB) is relatively low. Consequently, these organisms are often not empirically covered. However, in many hospitals, extended-spectrum beta-lactamase (ESBL)–producing *Enterobacterales* are relatively common (in 2020, 24.7% of *E. coli* isolates from US healthcare–associated infections were resistant to extended-spectrum cephalosporins [36]), as are strains of *P. aeruginosa* that are not DTR; in critically ill patients with relevant risk factors, empiric coverage for these pathogens should be considered [1, 37]. For serious infections known or suspected to be caused by MDR-GN bacteria, treatment guidelines recommend empiric antibiotic treatment with 2 anti-pseudomonal antimicrobial agents from different classes [14], such as an aminoglycoside plus an anti-pseudomonal beta-lactam, taking into account the site of infection, local antibiogram data, and toxicities of available therapies. Due to the updated Clinical and Laboratory Standards Institute (CLSI) breakpoints for aminoglycosides, options are now limited mainly to tobramycin and plazomicin, depending on the local antibiogram [38]. Clinicians should communicate with their clinical microbiology laboratory to determine if the most recent CLSI breakpoints have been incorporated into the susceptibility reporting for aminoglycosides as well as other antimicrobial classes [38]. In addition, for patients at risk for CRE, DTRP, or CRAB, use of newer agents active against these pathogens can be considered. The decision of whether to provide empiric coverage for a specific type of MDR pathogen should be based on local antibiogram data and case-specific patient information, including acute severity of illness and risk factors [14]. The Infectious Diseases Society of America provides up-to-date recommendations on antibiotic choices for MDR-GN infections [5, 39].

After selecting an empiric regimen, antimicrobials should be dose-optimized with regard to patient, antimicrobial, and microbiological factors, taking into account the local susceptibility and minimum inhibitory concentration (MIC) data for the targeted pathogens [40]. This is especially important in critically ill patients where abnormal volume of distribution, hemodynamic fluctuations, and renal or liver dysfunction are common [40–43]. For patients with acute kidney injury (AKI), renal function should be closely monitored, and changes in renal function should be considered when determining antibiotic dosing [43, 44]. Some experts recommend no initial adjustments for renal dysfunction for at least 24 hours after antibiotic initiation, followed by clinical reassessment [44, 45]. For critically ill patients with a glomerular filtration rate greater than 25 mL/min/1.73 m^2, it is reasonable to initially administer antibiotics at usual non-renally adjusted doses with close monitoring. Exceptions to this include aminoglycosides and vancomycin because these antimicrobials can rapidly accumulate and cause nephrotoxicity. After appropriate loading doses have been administered for aminoglycosides and vancomycin, additional dosing should take into account renal function. In an attempt to treat MDR-GN pathogens with elevated MICs, we suggest antimicrobials be dose-optimized by using high doses and extended infusion times for anti-pseudomonal beta-lactams (such as cefepime, piperacillin-tazobactam, meropenem), when applicable [46, 47]. Traditional intermittent infusion of beta-lactam antibiotics results in high peak concentrations but short half-lives, leading to rapid drops in serum drug levels and decreased likelihood of optimizing the time above the MIC (fT > MIC), particularly for organisms with elevated MICs. Prolonging the infusion time provides more consistent serum levels and maximizes fT > MIC [47]. The clinical benefits of extended and prolonged infusion beta-lactams were demonstrated in a meta-analysis of 632 critically ill patients with severe sepsis that showed improved mortality (19.6% vs 26.3%) and clinical cure (55.4% vs 46.3%) in those who received continuous versus intermittent infusion beta-lactam antibiotics, respectively [48].

Therapeutic drug monitoring (TDM) is another tool that can be used to optimize antimicrobial dosing. A recent large study

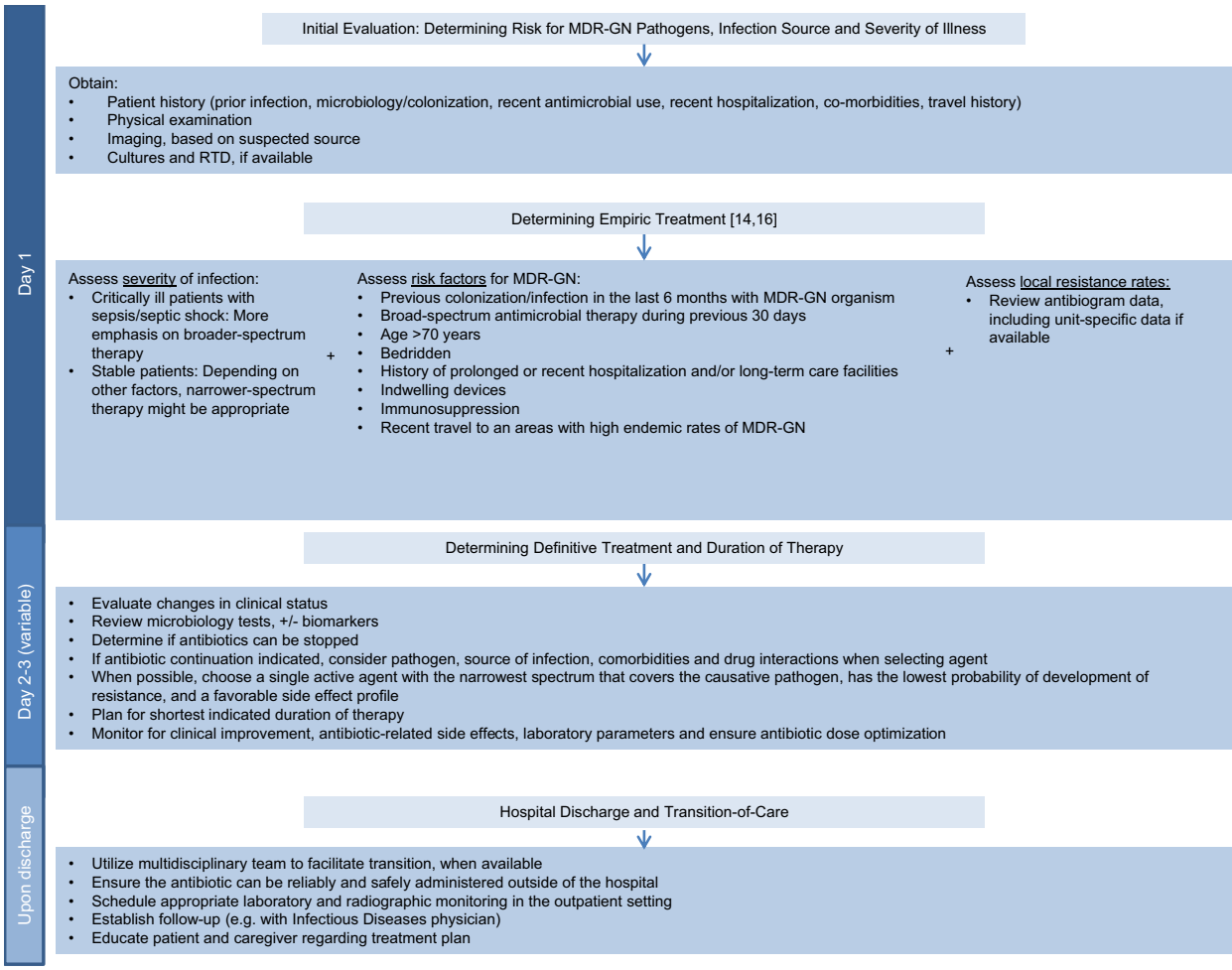


Figure 1. Recommended treatment algorithm for managing patients with suspected MDR-GN infections. Abbreviations: MDR-GN, multidrug-resistant gram-negative; RDT, rapid diagnostic testing.

that measured beta-lactam concentrations in critically ill patients revealed that many patients did not achieve pharmacokinetic/pharmacodynamic (PK/PD) targets, which could potentially affect clinical outcomes [49]. Unfortunately, the availability of TDM for commonly used beta-lactams is generally limited to research settings in the United States [40].

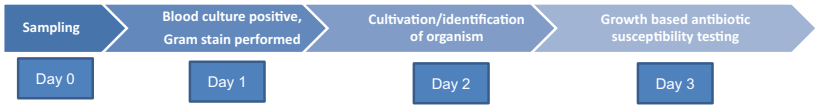
Patient Case Follow-up

Based on past and current signs, symptoms, and radiographic findings, it was determined that the patient likely had a respiratory source of infection. She had the following risk factors for MDR-GN infection: recent antibiotic exposure, previous culture/colonization with likely ESBL *E. coli*, and recent hospitalization. Potential GN pathogens that were considered included MDR-GN *Enterobacterales*, including ESBL, and non-DTR *P. aeruginosa*. The local nursing home antibiogram was unavailable, but the hospital antibiogram showed *P. aeruginosa* susceptibility to meropenem in the ICU to be 75%. Based on these risk factors, the patient being in septic shock, and the local antibiogram, the patient was started empirically on meropenem to cover the organisms identified in her history (the ESBL *E. coli* and susceptible *P. aeruginosa*) and a second GN agent, parenteral tobramycin, to provide additional GN coverage (*P. aeruginosa* susceptibility to tobramycin in the ICU was 85%). In addition, intravenous vancomycin was added due to her risk factors [35]. Since the patient did not have a past history of CRE, DTRP, or CRAB, the decision was made to not cover empirically for these pathogens.

TRANSITIONING FROM EMPIRIC TO DEFINITIVE THERAPY AND MONITORING CLINICAL RESPONSE

Once empiric therapy is started, diagnostic testing results including traditional cultures, gram stain results, and RDT results should be reviewed for opportunities to escalate or streamline antimicrobial therapy to the targeted or identified pathogen [50].

Timeline for Traditional Identification and Antibiotic Susceptibility Testing



Characteristics of Rapid Diagnostic Tests for Pathogens in Blood and Respiratory Specimens

Rapid diagnostic tests [52-54]	Resistance genes/organisms	Sample type	Day on which results available and time required to run assay
Genotypic susceptibility			
Multiplex PCR			
FilmArray® Blood Cultures Identification 2 (BCID2, Biofire®)	Identification of multiple bacteria, 7 yeasts and resistance genes: CTX-M, IMP, KPC, NDM, OXA-48 like, VIM, mcr-1, mecA/C, mecA/C and MREJ, vanA/B	Positive blood culture	Day 1, 1 hour
DNA Microarray			
Verigene® Gram-Negative (Luminex®)	Identification of 9 bacteria and resistance genes: CTX-M, KPC, IMP, NDM, OXA, VIM	Positive blood culture	Day 1, 2.5 hours
Magnetic resonance method after DNA hybridization			
T2Bacteria® (T2 Biosystems®)	Identification of 5 bacteria	Whole blood	Day 0, 3-5 hours
Multiplex PCR and DNA microassays			
GenMark ePlex® (GenMark Diagnostics, Inc.)	Identification of 21 bacteria, and resistance genes: CTX-M, IMP, KPC, NDM, OXA, VIM	Positive blood culture	Day 1, 1.5 hour
Fluorescence in-situ hybridization			
Gram-Negative QuickFISH (OpGen®)	Identification of *E. coli*, *P. aeruginosa*, and *K. pneumoniae*	Positive blood culture	Day 1, 0.3 hour
Rapid phenotypic susceptibility testing			
Time-lapse imaging of bacterial cells on dark-field microscopy. Antimicrobial susceptibility based on morphokinetic cellular analysis.			
Accelerate Pheno™ (Accelerate Diagnostics)	Identification of 16 bacteria and 2 yeasts with susceptibility results	Positive blood culture	Day 1, 1.5 hours (organism identification); 7 hours (susceptibility results)
Rapid identification			
Matrix-assisted laser desorption/ionization time-of-flight			
MALDI/TOF (Biomerieux, Bruker)	Identification of vast array of bacterial and fungal microbes	Positive blood culture	Day 1, 0.5 hour
Non-blood systems			
Multiplex PCR			
FilmArray® pneumonia panel (BioFire®)	Identification of 18 bacteria, 8 viruses, resistance genes: CTX-M, IMP, KPC, NDM, OXA-48 like, VIM, mecA/C, MREJ	Direct from respiratory culture	Day 0, 1 hour
Unyvero lower respiratory tract panel (OpGen®)	Identification of 19 bacteria, 1 fungi, resistance genes: CTX-M, KPC, NDM, OXA-23, OXA-24, OXA-48, OXA-58, TEM, VIM, mecA	Direct from respiratory culture	Day 0, 5 hours

Figure 2. Review of standard culture methods and summary of available gram-negative rapid diagnostic testing platforms. Abbreviations: CTX-M, cefotaxime-resistant beta-lactamase discovered in Munich; IMP, imipenemase; KPC, *Klebsiella pneumoniae* carbapenemase; MALDI/TOF, matrix-assisted laser desorption/ionization time-of-flight; mcr, mobilized colistin resistance; MREJ, mec right-extremity junction; NDM, New Delhi metallo-beta-lactamase; OXA, oxacillin-resistant beta-lactamase; PCR, polymerase chain reaction; VIM, Verona integron-encoded metallo-β-lactamase.

Traditional Microbiology Results

Traditional culture methods may take several days to yield susceptibility results. Although early microbiology results such as gram stain and enzymatic activity (eg, "lactose fermenter positive") can inform early treatment decisions, susceptibility results remain indispensable in MDR-GN infections [51]. Depending on the institution, broth microdilution susceptibility panels may be outdated (may not include updated CLSI breakpoints) or incomplete (may not include the newer agents and/or older agents such as the polymyxins), leading to delays in susceptibility results. We suggest communicating with the local microbiology laboratory to determine what panels are being used and if further testing is needed to include susceptibility data of newer agents. In such scenarios, additional manual susceptibility testing must be performed to test additional agents, prolonging the delay in obtaining full susceptibility information. These delays are particularly relevant in MDR-GN infections, as several of the newer approved agents have niches for

different resistant pathogens. Reflex testing can expedite the testing of newer agents for MDR-GN pathogens. For example, if a *Klebsiella pneumoniae* isolate tests resistant to carbapenems or if a carbapenemase is detected by RDT, the microbiology laboratory might preemptively "reflex test" the pathogen susceptibility for agents such as ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam, plazomicin, and cefiderocol before clinicians request that the testing be done. In hospitals where there are high rates of MDR-GN infections, novel antimicrobials, once approved and available for automated testing, may be included on automated panels.

Rapid Diagnostic Testing

RDT methods have significantly shorter turnaround times compared with traditional gold standard culture methods [12] and are particularly important in the management of MDR-GN infections. RDT can assist in earlier identification of organisms and resistance genes, improving time to effective therapy [50]. RDT accelerates the detection of causative organisms to guide directed therapy [50]. The turnaround time for RDT methods ranges from 1 to 8 hours, substantially shorter than traditional culture methods [52]. See Figure 2 for a summary of available RDT for GN organisms. RDT can be used for pathogen identification and genotypic and, in some cases, phenotypic detection of antibiotic resistance. RDT for bloodstream infections has shown promising benefits in improving the time to effective and optimal therapy, as well as clinical outcomes, including mortality, length of hospital stay, and recurrent bacteremia [55, 56]. More data on the impact of RDT on respiratory, central nervous system, and gastrointestinal infections are needed [57]. Since RDT results may not be acted upon in a timely manner or may be difficult for non-ID practitioners to interpret, we suggest pairing RDT testing with real-time interventions by ID or AS groups. It is important to recognize that RDT platforms are not universal, and some institutions may not have in-house access to these rapid diagnostic tools. In such cases, alternatives include using external laboratories for resistance gene testing on specific isolates or establishing workflows for improving the rapidity of susceptibility testing of newer agents on select organisms. These processes should be developed collaboratively by a local multidisciplinary group that consists of ID, AS, and microbiology experts.

Definitive Therapy

Once microbiology results become available, definitive therapy should be tailored accordingly, in most cases, using a single active agent with the narrowest spectrum that covers the causative pathogen and has the lowest probability of developing in vivo resistance and side effects [14]. Other important considerations in the selection of the definitive therapy include comorbid conditions (eg, hepatic insufficiency or renal injury), site of infection, severity of clinical presentation, and medication allergies or intolerances. Antimicrobial dosing should be optimized based on accepted PK/PD principles and specific drug properties [13]. Additionally, interpretation of susceptibility patterns in MDR-GN pathogens can be nuanced. Even when, based on in vitro susceptibility, narrower antibiotic options may be active, they may not beideal therapeutic choices (eg, third-generation cephalosporins should be avoided in patients with infections due to *Enterobacter cloacae* regardless of third generation cephalosporin susceptibility results) based on in vitro susceptibility, narrower antibiotic options may be active [5, 39]. Therefore, when a pathogen is confirmed as an MDR-GN, consultation with ID/AS experts is advised [14].

Clinical Response

Monitoring treatment response in MDR-GN infections is crucial, given that newer antimicrobials used for these infections are often used off-label or in patient populations not studied in clinical trials [57]. Determining the anatomic source of infection is also important as this will influence the way response to therapy is monitored. Vital signs, microbiologic clearance, hemodynamic stability, changes in relevant imaging, and achievement of source control are key factors associated with treatment response. Biomarkers such as lactate and procalcitonin are sometimes used, although their utility is still debated [58–60].

Development of antimicrobial resistance while on therapy can occur with GN infections, particularly infections that are subacute or chronic in nature. In cases where patients show no clinical improvement, it is important to ensure that antimicrobial therapy is optimized, new cultures have been obtained, repeat imaging has been considered, and additional sources of infection have been assessed, including noninfectious causes of clinical failure. An escalation antibiogram can assist in decision-making when current therapy is ineffective and can be used by providers to select antibiotics with an increased likelihood of activity when multidrug resistance is observed [61]. The concept of an escalation antibiogram was introduced by Teitelbaum et al, who created antibiograms for 12 commonly used antibiotics for GN bacteremia. When resistance was present to a given antibiotic for each GN pathogen, the antibiograms presented the likelihood of susceptibility to 11 alternative agents [61]. In select critically ill patients with MDR-GN risk factors where the diagnostic workup is negative, we suggest considering deescalating the antimicrobials (if concerned for infection without MDR-GN) or discontinuing antimicrobials (if infection is no longer suspected), as noninfectious causes of systemic inflammatory response syndrome are common [62, 63]. This is where ID consultation would be particularly important in helping make these decisions.

Duration of Treatment

The decision regarding duration of treatment should take into account the severity of the initial illness and response to treatment, certainty of diagnosis, type/location of infection, whether source control has been obtained, and medication side effects. The presence of MDR-GN pathogens or antimicrobial resistance alone should not impact the treatment duration [5, 39]. Shortening treatment duration is an effective approach for reducing antibiotic resistance by minimizing selective pressure on the endogenous microflora [64]. Longer durations of therapy are associated with increased likelihood of selecting for resistance, higher risk for developing drug-induced adverse events, and higher costs. Clinical studies suggest that shorter treatment durations are safe and do not increase the likelihood of treatment failure [65–72]. In some studies, procalcitonin, which is a precursor of the hormone calcitonin, has been demonstrated to be effective in guiding duration of therapy in pneumonia [60].

Patient Case Follow-up

Following initiation of antibiotics, the patient remained febrile and remained on norepinephrine with stable ventilator requirements. Eight hours after initiation of antibiotics, blood cultures returned with 2 sets positive for GN bacilli. RDT results, which were available 1 hour later, showed *K. pneumoniae* with the *KPC* gene detected. The hospital AS team, which intervenes on all positive RDT results, recommended switching the antibiotic regimen to meropenem-vaborbactam that was dose-optimized and recommended an ID consult. Two days later, susceptibility results confirmed the organism was resistant to standard antimicrobials (including meropenem) but was susceptible to tobramycin (based on updated CLSI breakpoints). Because the organism was resistant to meropenem, reflex susceptibility testing was done, and results indicated susceptibility to ceftazidime-avibactam, imipenem-cilastatin-relebactam, and meropenem-vaborbactam. Additional agents such as cefiderocol and plazomycin were not tested. Respiratory cultures later produced a carbapenem-resistant *K. pneumoniae*. Over the next 72 hours, the patient became afebrile, was extubated, had a decreased WBC to $11 \times 10^3/\mu L$, had resolved the AKI, and was downgraded to the medical ward. Per ID recommendations, a 7-day course of meropenem-vaborbactam was chosen for GN bacteremia from a pulmonary source as the patient had improved quickly with effective antibiotic treatment.

MONITORING ANTIMICROBIAL-RELATED PARAMETERS

Antimicrobials are often associated with side effects. In a retrospective cohort study of 1488 patients, 298 (20%) patients experienced at least 1 antibiotic-associated adverse event. The most common were gastrointestinal, renal, and hematologic abnormalities [73]. Laboratory monitoring for patients who are being treated for an infection due to an MDR-GN organism usually includes a basic metabolic panel for renal function and electrolyte monitoring,and a complete blood count for response to therapy and cytopenia monitoring. These are typically assessed daily for inpatients and weekly for outpatients [74, 75]. Some additional monitoring requirements are class-specific, including ototoxicity and TDM for select antimicrobials including the aminoglycosides [74].

TRANSITIONS OF CARE AND DISCHARGE CONSIDERATIONS

Complex outpatient antimicrobial therapy, which includes OPAT and oral antimicrobials used for extended periods, may be required for certain patients with MDR-GN infections. When transitioning a patient to outpatient antibiotic treatment, key considerations include administration convenience, minimizing the number of medications/dosing frequency, and optimizing safety and tolerability for better adherence [76]. The location where treatment will be administered post-discharge is important as it can influence adherence. Antibiotics that require less frequent daily dosing are favorable [74, 76]. One study found OPAT regimens dosed once or twice daily were more closely associated with adherence compared with more frequent regimens [77]. To facilitate less frequent dosing and to maximize chances of PK/PD target attainment, certain beta-lactams such as ceftolozane-tazobactam can be given as a continuous infusion [76–79]. Whenever possible, oral therapy should be considered for post-discharge treatment; this will obviate the need for an intravenous catheter and associated complications [76, 80]. However, this is often not feasible for MDR-GN infections [81, 82].

The antimicrobial regimen should be reviewed by an ID consultant prior to discharge to aid in appropriate regimen selection and scheduling outpatient follow-up [74, 76]. Patients and family members should receive education on antibiotic administration, potential side effects, and necessary follow-up, which improves the comfort level of family members and patients with regard to home infusions [76, 83]. The regimens used to treat MDR-GN infections are often more costly than traditional regimens and may not be readily available. The availability of the agent, its cost, and insurance coverage should be reviewed, ideally with the help of healthcare professionals who are familiar with these logistics, such as case managers and pharmacists, to ensure that patients can afford and obtain the prescribed antimicrobials on discharge. A multidiscipline discharge approach can streamline the transition of care and reduce readmissions [76, 84].

After discharge, patients should have early follow-up with an ID specialist, ideally within 2 weeks, for timely detection and management of treatment failure or adverse events [74, 76, 85]. Patients often require outpatient laboratory monitoring [74, 76]. For patients on OPAT, non-availability of monitoring

test results to ID physicians was independently associated with hospital readmission (adjusted odds ratio, 2.53; 95% confidence interval, 1.36–4.73) [86]. Depending on the laboratory testing and monitoring that is required, antimicrobial dosing schemes may have to be adjusted to coincide with blood sampling needed for TDM (eg, aminoglycosides may have to be dosed later in the day, depending on the timing of blood specimens needed for accurate TDM) [74, 76].

Patient Case Follow-up

With clinical improvement, transfer back to the nursing home on hospital day 5 was planned. After consultation with a social worker and case manager, the patient was accepted back to her nursing home. However, the facility did not have meropenem-vaborbactam available but had ceftazidime-avibactam on formulary. After discussions with the ID consultant, therapy was changed to ceftazidime-avibactam to facilitate discharge. A multidisciplinary team was involved in the discharge planning, which included ensuring that the nursing home had the recommended antibiotic and appropriate monitoring capabilities. An appointment was made for follow-up with the ID consultant at the clinic, insurance and cost coverage was ensured, and the patient and the patient's family were educated regarding the plan of care.

CONCLUSIONS

The treatment of MDR-GN infections is complex, especially in severe and life-threatening cases. Several newer antimicrobial agents that are active against MDR-GN infections have become available, providing additional therapeutic options. Given the importance of these new antibiotics, protocols should be implemented to optimize their use. When making therapeutic decisions, several factors need to be considered, including recognizing risk factors for MDR-GN pathogens, improving diagnosis through phenotypic and molecular resistance typing techniques, modifying therapy appropriately, and avoiding unnecessarily long durations of antibiotic therapy. Transition of care can be complex, and multidisciplinary teams can facilitate planning and post-discharge care.

Note

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