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Review Article

Gaps in the Guidelines: Empiric Treatment of Multidrug Resistant Organisms

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ABSTRACT

Multidrug Resistance (MDR) is defined as acquired non-susceptibility to at least one agent in three or more antimicrobial classes or resistance to one key antimicrobial agent. Infections caused by Multidrug Resistant Organisms (MDROs) have an increased risk of inpatient mortality, morbidity and are associated with prolonged hospitalization and higher risk of readmission. MDROs are an independent risk factor for inpatient mortality and the risk of this is heightened with delays in appropriate antibiotic therapy. While there are published guidelines that outline targeted treatments of MDROs, guidance on when to empirically treat MDROs, both initially and upon readmission, is lacking. Healthcare providers must balance the risk of delaying appropriate antibiotics with the risk of increasing antimicrobial resistance with overuse of broad-spectrum antibiotics.

Keywords: Multidrug resistant organisms; Empiric treatment; Targeted treatment

INTRODUCTION

In 2011, standard international terminology was created for *Staphylococcus aureus*, *Enterococcus* spp., *Enterobacteriaceae* (other than *Salmonella* and *Shigella*), *Pseudomonas aeruginosa* and *Acinetobacter* spp. resistance profiles through a joint initiative by the European Center for Disease Prevention and Control (ECDC) and the Centers for Disease Control and Prevention (CDC). Through this initiative, Multidrug Resistance (MDR) was defined as acquired non-susceptibility to at least one agent in three or more antimicrobial classes or resistance to one key antimicrobial agent. Organisms considered to have extreme or Extensive Drug Resistance (XDR) are non-susceptible to one or more agents in all but two or fewer antimicrobial classes. Pan Drug Resistant (PDR) organisms are considered resistant to all antimicrobial agents or all commercially available antimicrobials. Infections caused by Multidrug Resistant Organisms (MDROs) in the hospital have an increased risk of mortality, morbidity, prolonged hospitalizations and hospital readmissions compared to those caused by organisms without resistance mechanisms. It is estimated that over 2 million patients will isolate a MDRO each year, in the United States and 23,000 will die as a result of their infection. Although risk factors have been identified to help predict patients at risk for MDROs, recommendations on empiric therapy for MDROs is lacking [1].

The "ESKAPE" pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter* species) were the first organisms described as multidrug resistant and are still the leading cause of multidrug resistant infections. Concern for emerging MDROs grew with the discovery of carbapenem-resistant pathogens, most commonly *A. baumannii* (CRAB), *P. aeruginosa* (CRPA), *Enterobacterales* (CRE). MDROs can be grouped both by their resistance mechanism and their gram stain.

LITERATURE REVIEW

Gram-positive MDROs

Gram-positive MDROs include methicillin-resistant *S. aureus* and Vancomycin-Resistant *Enterococcus* (VRE). MRSA currently accounts for about 25% of all *S. aureus* isolates, but prevalence is much higher in some areas. Methicillin resistance in MRSA is due to the expression of both a β-lactamase and the *mecA* gene which encodes for the Penicillin-Binding Protein 2a (PBP2a). PBP2a prevents b-lactam antibiotics from inhibiting bacterial cell wall synthesis, their primary mechanism of action [2]. The majority of the time MRSA is treated with glycopeptide antibiotics such as vancomycin. However, in the case of vancomycin-intermediate and vancomycin-resistant *S. aureus*

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isolates (VISA and VRSA), antibiotics such as linezolid, daptomycin and ceftaroline are preferred. Although there are many species of *Enterococcus*, *E. faecium* and *E. faecalis* account for the overwhelming majority of MDR Enterococcal infections. Vancomycin resistance is most associated with *E. faecium*. Resistance is inferred by the van genes (*van A, B, D, E, G, C1, C2* and *C3*), the most prevalent being vanA. The *vanA* gene alters the binding site of vancomycin on the cell wall, which prevents a strong bond of vancomycin to the organism. VRE is commonly treated with non-glycopeptide antibiotics such as linezolid and daptomycin [3].

Gram-negative MDROs

The Infectious Disease Society of America's (IDSA) 2024 guidance on the treatment of antimicrobial-resistant gram-negative infections groups gram-negative MDROs into six categories: Extended-Spectrum β-Lactamase-producing *Enterobacterales* (ESBL-E), AmpC β-Lactamase-producing *Enterobacterales* (AmpC-E), Carbapenem-Resistant *Enterobacterales* (CRE), difficult to treat *Pseudomonas aeruginosa* (DTR *P. aeruginosa*), Carbapenem-Resistant *Acinetobacter baumannii* (CRAB) and *Stenotrophomonas maltophilia*. ESBLs, most commonly CTX-M, confer resistance against most penicillin and cephalosporin antibiotics by hydrolyzing the β-lactam ring. ESBLs can be carried by any gram-negative organism, however they are commonly isolated in *Escherichia coli*, *Klebsiella pneumoniae*, *Klebsiella oxytoca* and *Proteus mirabilis*. ESBL-producing organisms are typically susceptible to carbapenems as well as other non-β-lactam antibiotics that treat gram-negative infections (fluroquinolones, aminoglycosides, etc.) [4]. AmpC β-lactamases are a subset of β-lactamases that hydrolyze first, second and third generation cephalosporins, as well as penicillin antibiotics. Exposure to these antibiotics can induce ampC production and therefore cause organisms with original susceptibility to become resistant during the course of treatment. Inducible ampC production is most notable in Enterobacter cloacae complex, *Klebsiella aerogenes* and *Citrobacter freundii*. CREs are Enterobacterales that are resistant to at least one carbapenem antibiotic or one carbapenem other than imipenem in organisms that are intrinsically non-susceptible to imipenem. CREs are a large group of organisms with many resistance genes, including *K. pneumoniae carbapenemases* (KPC); metallo-β-lactamases such as New Delhi Metallo-β-Lactamases (NDMs), Verona Integron-encoded Metallo-β-Lactamases (VIMs), Imipenemhydrolyzing Metallo-β-Lactamases (IMPs); and oxacillinases (*i.e.*, OXA-48-like). Carbapenem resistance is conferred through various mechanisms including production of carbapenemases, increased efflux pump action and decreased antibiotic permeability through the bacteria cell wall. The preferred treatment for infections caused by CREs varies depending on the source. Urinary tract infections caused by CREs can be treated with nitrofurantoin, SMX-TMP, fluorquinolones like ciprofloxacin or levofloxacin and aminoglycosides like gentamicin, depending on the severity of the infection. Treatment of non-urinary infections caused by CREs is dependent on the type of CRE isolated. Generally, meropenem-vaborbactam, ceftazidime-avibactam and imipenem-cilastatinrelebactam are options, especially in KPC producing organisms [5]. MDR *P. aeruginosa* is *P. aeruginosa* isolates that are not susceptible to at least one antibiotic in at least three antibiotic classes of which *P. aeruginosa* is typically susceptible. DTR *P. aeruginosa* are isolates that are not susceptible to piperacillin-tazobactam, ceftazidime, cefepime, aztreonam, meropenem, imipenem-cilastatin, ciprofloxacin and levofloxacin. This enhanced resistance to *Pseudomonas* occurs through multiple mechanisms including decreased outer membrane porins, pseudomonal AmpC enzyme production, upregulation of efflux pumps and others. Due to the number of mechanisms conferring enhanced resistance to *P. aeruginosa* treatment is guided by susceptibility data. In the case of *P. aeruginosa* isolates that show susceptibility to non-carbapenem β-lactams and carbapenem agents, treatment is preferred with non-carbapenem antibiotics through high-dose extended-interval administration. In the case of *P. aeruginosa* isolates that show susceptibility to non-carbapenem β-lactams but resistance to carbapenems, the use of ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-cilastatin-relebactam should be considered if susceptible. CRAB confers additional resistance to carbapenems in addition to the acquired resistance already present in *A. baumannii* isolates. The preferred treatment for CRAB includes a sulbactam-containing antibiotic in combination with a carbapenem. In the case sulbactam-durlobactam is not available, treatment with high-dose ampicillin-sulbactam in combination with one other agent (polymyxin B, minocycline or cefiderocol) is an alternate treatment approach. *Stenotrophomonas maltophilia* isolates carry two specific β-lactamases that hydrolyze penicillins, cephalosporins, aztreonam and carbapenems. Other resistance mechanisms such as multidrug efflux pumps reduce the susceptibility to SMX-TMP, tetracyclines and fluorquinolones [6]. Although there is no standard of care in terms of treating *S. maltophilia* infections, guidelines recommend double coverage with two of the following: Cefiderocol, minocycline, SMX-TMP or levofloxacin. Combination therapy with ceftazidime-avibactam and aztreonam is reasonable as well, depending on susceptibility data for the isolate.

MDROs are an independent risk factor for inpatient mortality, especially when appropriate susceptible antibiotic initiation is delayed. Early detection and treatment of MDROs can mitigate this risk. Many risk factors for MDROs have been identified. Regarding pneumonia, IDSA states that MDROs should be considered in patients with prior isolation of such organisms, recent hospitalization and recent antibiotic use. These can likely be extrapolated to other sources of infection as well. Additional validated risk factors include mechanical ventilation, ICU level of care, prolonged hospital length of stay, invasive procedures, use of acid suppression medications and pre-existing pulmonary disorders. Despite the many risk factors identified for MDROs, few guidelines make official statements on how and when to empirically treat for these organisms [7].

IDSA lacks definitive antimicrobial recommendations for empiric therapy as they state that decisions for empiric treatment of MDROs are outside the scope of their guidelines. Instead, they focus on the importance of evaluating patient-specific factors and prior antimicrobial history to guide treatment. These guidelines recommend targeting MDR gram-

negative organisms by the likely pathogen, illness severity, infection source and other relevant patient-specific factors. Moreover, there is an emphasis in evaluating past culture results and Antimicrobial Susceptibility Testing (AST) in the past 12 months, antibiotic use in the past 3 months and local AST patterns. IDSA emphasizes the goal to streamline treatment based on AST, identified pathogen and the presence of any prominent β-lactamase genes; however, many institutions do not have access to this data until hours or days after empiric therapy has been initiated. Distinguishing between colonization and infection is important for highly resistant pathogens like DTR *P. aeruginosa*, CRAB and *Stenotrophomonas maltophilia*, as inappropriately including antibiotics susceptible to these MDROs in initial empiric regimens may increase risk for additional resistance development and antibiotic-related adverse events. For these reasons, empiric treatment of CRAB and *S. maltophilia* is generally discouraged, unless decided to be necessary after a risk-benefit analysis [8].

There are conclusive recommendations for empiric treatment of MRSA depending on the source of infection. Patients with severe Community-Acquired Pneumonia (CAP) or Hospital-Acquired Pneumonia (HAP) should receive empiric treatment for MRSA if they have had prior respiratory isolation of MRSA, have been hospitalized or received Intravenous (IV) antibiotics in the past 90 days. Those with suspected Ventilator-Associated Pneumonia (VAP) should receive empiric MRSA treatment if they are located in a unit where >10-20% of *S. aureus* is MRSA; if the unit in which they are located has an unknown prevalence of MRSA; or if they have additional risk factors for MDR VAP including prior IV antibiotic use, septic shock at the time of VAP onset, Acute Respiratory Distress Syndrome (ARDS) preceding VAP diagnosis, five or more days of hospitalization or acute renal replacement therapy prior to VAP onset. SSTIs requiring inpatient management should be empirically treated for MRSA until culture data warrants de-escalation. Research gaps exist for the utility of anti-MRSA empiric therapy in other moderate-severe infections like bacteremia and endocarditis [9].

DISCUSSION

There are gaps in published infectious disease guidelines on the empiric treatment of MDROs in general and although IDSA states that healthcare providers should consider relevant culture and AST data from the past 12 months, there are no formal recommendations on how to empirically treat a patient with a historic MDRO upon readmission. A retrospective study in 2022 found that 68% of patients with a history of a gram-negative MDRO isolated a MDRO upon readmission to the hospital. This study took this observation to conclude that a history of MDROs alone does not justify the use of broad-spectrum antibiotics empirically, especially if the source of infection is not consistent between admissions. However, due to the observational nature of this study, it did not track clinical outcomes in patients who received empiric broad-spectrum antibiotics compared to those who did not. A 2024 study looked at patients with a historical MDRO and compared clinical outcomes in those who were empirically treated for their historic MDRO on admission with those who were not. It found a 6.5-day reduction in hospital length of stay when historic gram-negative MDROs were empirically treated upon admission as opposed to waiting for AST data to escalate or de-escalate therapy. This length of stay reduction was not replicated in patients with a historic gram-positive MDROs. Both of these studies were limited by sample size and neither can provide conclusive guidance for the empiric treatment of MDROs upon readmission in patients who have previously isolated a MDRO.

Neither of the above studies take bacterial colonization into consideration for determining when to empirically treat MDROs. Patients with a history of MDRO infection can become colonized with the causative bacteria even after appropriate treatment. A historic MDRO may cause a healthcare provider to initiate empiric broad spectrum treatment in patients that are readmitted to the hospital. Although this practice cannot be evaluated for efficacy or safety due to literature and guideline gaps, it is important to note that these patients may be colonized with their historic MDRO rather than acutely infected. Lack of clinical judgement in these situations may lead to overuse of broad-spectrum antibiotics. The MOSAR-ICU trial published in 2014 attempted to determine the length of which a patient with a historic MDRO may be colonized with the same bacteria after hospital discharge. This trial found that 50% of patients with a historic MDRO had lost colonization about 5 months after original isolation [10].

Overuse of broad spectrum broad-spectrum antibiotics can lead to collateral damage or negative ecological effects of antibiotic therapy contributing to increasing antimicrobial resistance. Antibiotics can induce resistance through many mechanisms, such as extrachromosomal plasmid DNA transfer (horizontal transfer), cell division (verticlevertical transfer), cell permeability alterations and others. Multiple studies have shown how antibiotic use can effect the susceptibility of previously non-resistant organisms and this coloration was validated in a 2014 meta-analysis. Increased use of antibiotics enables development of antibiotic resistance in the individual being treated, as well as greater antibiotic resistance for the overall community. This risk of collateral damage must be weighed with the risk of delaying appropriate antibiotics to infected patients. It is likely that a lack of guidance and literature exists on the empiric treatment of MDROs because the decision requires a careful, patient-specific risk-benefit analysis that cannot be easily generalized from one patient scenario to another.

CONCLUSION

In 2011, the European Center for Disease Prevention and Control (ECDC) and the Centers for Disease Control and Prevention (CDC) established standardized terminology for describing resistance profiles in bacteria such as *Staphylococcus aureus*, *Enterococcus* spp., *Enterobacteriaceae*, *Pseudomonas aeruginosa* and *Acinetobacter* spp. MDROs are associated with increased morbidity, mortality and prolonged hospitalizations. Despite identifying risk factors for MDROs and the need for targeted treatment, guidelines for empiric therapy remain underdeveloped. The "ESKAPE" pathogens are leading causes of MDRO infections, with growing concern over carbapenem-resistant strains. Treatment recommendations vary based on

specific resistance mechanisms and bacterial classification. Healthcare providers should emphasize the importance for timely, data-driven decisions to balance effective treatment and minimize resistance development. The lack of definitive guidelines for empiric treatment highlights the complexity of managing MDRO infections, requiring ongoing research and tailoring treatment based on individual patient factors and local resistance patterns.

REFERENCES

1. Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: An international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect. 2012;18(3):268-281.
2. Barrasa-Villar JI, Aibar-Remón C, Prieto-Andrés P, Mareca-Doñate R, Moliner-Lahoz J. Impact on morbidity, mortality and length of stay of hospital-acquired infections by resistant microorganisms. Clin Infect Dis. 2017;65(4):644-652.
3. Santajit S, Indrawattana N. Mechanisms of antimicrobial resistance in ESKAPE pathogens. Biomed Res Int. 2016:2475067.
4. Stogios PJ, Savchenko A. Molecular mechanisms of vancomycin resistance. Protein Sci. 2020;29(3):654-669.
5. Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious diseases society of America 2023 guidance on the treatment of antimicrobial resistant gram-negative infections. Clin Infect Dis. 2023:ciad428.
6. Shaikh S, Fatima J, Shakil S, Rizvi SM, Kamal MA. Antibiotic resistance and extended spectrum beta-lactamases: Types, epidemiology and treatment. Saudi J Biol Sci. 2015;22(1):90-101.
7. Bartal C, Rolston KV, Nesher L. Carbapenem-resistant Acinetobacter baumannii: colonization, infection and current treatment options. Infect Dis Ther. 2022;11(2):683-694.
8. Metlay JP, Waterer GW, Long AC, Anzueto A, Brozek J, Crothers K, et al. Diagnosis and treatment of adults with community-acquired pneumonia. Am J Respir Crit Care Med. 2019;200(7):e45-e67.
9. Wu C, Lu J, Ruan L, Yao J. Tracking epidemiological characteristics and risk factors of multi-drug resistant bacteria in intensive care units. Infect Drug Resist. 2023;16:1499-1509.
10. Kalil AC, Metersky ML, Klompas M, Muscedere J, Sweeney DA, Palmer LB, et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the infectious diseases society of America and the American thoracic society. Clin Infect Dis. 2016;63(5):e61-e111.