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Management of Multidrug-Resistant (MDR) Bacterial Infection in Patients Admitted to Surgical Ward: A Narrative Review

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Abstract

Multidrug-resistant (MDR) bacterial infections pose a formidable challenge in the management of patients admitted to surgical wards, necessitating a comprehensive and multifaceted approach. This narrative review delves into the intricate landscape of MDR bacterial infections within surgical settings, providing insights into their epidemiology, risk factors, diagnostic strategies, and therapeutic interventions. The emergence and proliferation of MDR bacteria, characterized by resistance to multiple classes of antibiotics, have raised concerns globally. Surgical patients, already vulnerable due to their underlying conditions, are particularly at risk for these infections, which can complicate postoperative recovery and even become life-threatening. Understanding the epidemiology of MDR bacterial infections in surgical wards is crucial. Patients with prolonged hospital stays, prior antimicrobial exposure, and invasive procedures are more susceptible. Rapid and accurate diagnostic methods, including molecular techniques and susceptibility testing, are essential for identifying MDR pathogens and tailoring treatment. Treatment options for MDR bacterial infections are limited and often involve last-resort antibiotics, such as colistin and carbapenems. Combining antimicrobial agents and source control measures like surgical debridement are common strategies. Additionally, antimicrobial stewardship programs play a pivotal role in optimizing antibiotic use, preventing resistance, and improving patient outcomes. Infection prevention and control measures, including strict hand hygiene, isolation protocols, and environmental cleaning, are indispensable for curbing the spread of MDR pathogens within surgical units. This narrative review provides a comprehensive overview of the challenges posed by MDR bacterial infections in surgical patients and emphasizes the need for a multidisciplinary approach involving surgeons, infectious disease specialists, microbiologists, and pharmacists. By implementing evidence-based strategies, healthcare providers can enhance patient care, minimize the impact of MDR infections, and contribute to global efforts in combating antimicrobial resistance.

Keywords: Infection control, Surgery, Admission, Prevention, Treatment.

Introduction

Multi-drug resistant (MDR) bacteria is a bacterium that is resistant to many kinds of antibiotics thus very hard to treat, leaving few (one or maybe two) antibiotics to treat the targeted infections. They are present in patients who have a low immunity profile, injured or staying in the hospital [1]. Anti-microbial resistance is a global issue that raises the importance of collaboration between countries trying to eradicate this massive health concern by ensuring that antibiotics should never be used unless it's necessary and when it's advised to be used, a clinician should choose the correct type of anti-microbial for the right infection to the optimal dose. Thus Practitioners role went beyond just prescribing the anti-biotic to preserve their effectiveness for now and future use [2]. This massive economic and health issue become a serious public health problem because no matter how well the country is equipped to face it there will be a crack through the system that allow its presence which represented by trading lines and travelling from country to another [2] [3]. AGORA project is the Global Alliance for Optimizing their Rational Use in Intra-Abdominal Infections, mainly it's tackling the MDR problem in 79 diverse countries, and these countries submitted a document regarding the awareness of rational use of antibiotics among Intra-Abdominal Infections patients [2]. The World Health Organization (WHO) is making a great effort to raise the awareness all over the globe about MDR bacteria and its impact on the world.[2] [5] because of this impact this problem may lead to increase the patients stay in hospital and these infections may become hard to treat [2] [3] [4]. Bacteria that modified and manipulate its structure make it difficult for anti-bacterial agents to kill them. Basically, anti-biotic exerts its action by indulging its self in the bacteria in different ways, for instance it penetrates the structure of the membrane (daptomycin), or interfere in the pathway of bacterial metabolism (trimethoprim-sulfamethoxazole), disrupts the genetic material synthesis (fluoroquinolones), inhibit the synthesis of the protein (macrolides), and interrupt the integrity of the cellular membrane (beta-lactams). Taking the gene from other resistant bacteria by many mechanisms is one of the ways by which it acquires the antibiotic resistance characteristic, or by having a mutation in the genes, yielding in enzymes that terminates the anti-microbial drug, avoiding the medication by creating a new way of attacking cells, if the drug exerts its effect inside the bacterial cell it may develop an exit pathway for the drug, changing the receptor binding place on the bacterial cellular membrane .these mechanisms and more makes the bacteria un affected by one or more kind of drugs [6].

Resistance in the ICU:

A comparison between UK and USA multi drug resistance tendencies both in the ICU and normal wards of the same hospital, giving a list of 8 MDR GNB Haemophilus influenzae, Enterobacterspp, E. coli, Klebsiella spp, Proteus mirabilis, P aeruginosa, Serratia spp, Acinetobacter spp., [7] resistance percentage was higher in the ICU compared to normal hospital wards. Extended-spectrum b-lactamase-ESBL producing strains of E coli (11.9% -17.4%) and Klebsiella spp percentage increases in the ICU of both USA and Europe with more increase in Europe during 3 years study (2009 – 2011) [7]. Susceptibility of Klebsiella spp., to hospital-associated BSIs (blood stream infections)survey (2001-2009) conducted in Europe concluded in that the resistance increases in both E. coli and S. aureus species, with a decline in S. aureus from 2005-2009 [8] [9].

Gram-negative bacilli resistance mechanisms:

The MDR in GNB issue in the ICU represents a critical daily problem that needs to be addressed in a sensitive way. Plasmid-borne extended-spectrum beta-lactamase (ESBL) produced by the Enterobacteriaceae are the main cause of the third-generation cephalosporin's resistance that's why Carbapenems are considered the first-line choice. On the other hand, some enzymes appeared during the last few decades that could affect the ability of carbapenems. KPC and OXA-48, NDM- and VIM type metallo-beta-lactamases, are Carbapenemase-generating strains that

is appeared lately. Unfortunately this might affect carbapenems sensitivity. ESBL- and carbapenemase-encoding plasmids frequently bear resistance determinants for other antimicrobial classes, including aminoglycosides (aminoglycoside-modifying enzymes or 16S rRNA methylases) and fluoroquinolones (Qnr, AAC(6′)-Ib-cr or efflux pumps), a key feature that fosters the spread of multidrug resistance in Enterobacteriaceae.

In non-fermenting GNB such as Pseudomonas aeruginosa, Acinetobacter baumannii and Stenotrophomonas maltophilia, multidrug resistance may emerge following the sole occurrence of sequential chromosomal mutations, which may lead to the overproduction of intrinsic beta-lactamases, hyper-expression of efflux pumps, target modifications and permeability alterations. P. aeruginosa and A. baumannii also have the ability to acquire mobile genetic elements encoding resistance determinants, including carbapenemases. These carbapenem-resistant GNB are considered very hard to treat leaving the problem with rare options also colistin resistance emerged as a very critical issue [6].

Latest Guidelines of gram negative treatment

Carbapenems:

Carbapenems are first line therapy for bacteremia caused by gram negative species, especially ESBL-producing ones [10].

Meropenem and imipenem/cilastatin used for carbapenem resistant GNB, especially carbapenem-resistant A. baumannii. Urine Enzymatic degradation that occur to imipenem is rendered by cilastatin. Meropenem is better than cilastatin/imipenem [11], but both of them are considered superior to ertapenem.

Ertapenem

It is a medication that is used once daily and that is a beneficial feature. It is active against anaerobic bacteria, Enterobacteriaceae, several gram positive strains [12]. Acinetobacter spp. And P. aeruginosa are exerting resistance against Ertapenem. Used for urinary tract infections, pneumonia, gynecological and abdominal infections.

Meropenem+vaborbactam:

Are in Phase 3 as clinical trial, it raises hopes about Enterobacteriaceae species that produce KPC carbapenemases but not those with MBLs or OXA-like enzymes [13,14, 1].

Eravacycline:

Eravacycline is derived from tetracycline, developed to overcome vancomycin-resistant Enterococci. ESBL, MRSA and CRE resistance. Giving high rate of cure for complicated intraamniotic infection syndrome and urinary tract infections, fortunatly it demonestrated mild to moderete side effects (nausea) (11%-22%) [15].

Ceftazidime/avibactam:

Avibactam restores ceftazidime activity against most carbapenemase-producing Enterobacteriacea, although, avibactam and all other β-lactamase inhibitors currently available for clinical use they do not inhibit metallo-β-lactamases (MBLs). U.S. Food and Drug Administration (FDA) approved ceftazidime-avibactam by in 2015 represented an important advancement in the treatment of infections caused by carbapenem-resistant Enterobacteriaceae.

Ceftolozane/tazobactam:

A combiation between Ceftolozane (oxyimino-cephalosporin) and tazobactam. Could be used to eradicate numerous kind of bacteria like Enterobacteriaceae, GNO and its considered the most effective b-lactam against P. aeruginosa [16].

Ceftolozane/tazobactam is approved at the recent time to br used for intra-abdominal sepsis and urinary tract infections that is appeared to be complicated. It is not to be used against KPC-producing Enterobacteriaceae or AmpC [17].

Aztreonam:

Azetreonam is an old drug that is used only when extremely needed to attack p. Aeruginosa because its still to some extend active against it [9], on the contrary using it empirically alone against KPC carbapenemase, ESBLs producing Gram-negative bacteria and AmpC is useless because it’s totally inactive [18]. Gram negative bacteria and post-neurosurgical meningitis: For the treatment of PNM post-neurosurgical meningitis caused by GNB, caphalosporins are preffered more than carbapenems because they are less prone to make side effect

(siezures). Meropenem (carbapenem) is the drug of choice when targeting ESBL-producing bacteria because we can use high doses of it and expect less side effect (convulsions) [19,20].

Conclusions

The high rate of PNM caused by carbapenem-resistant A. baumannii and Pseudomonas aeruginosa, has led to the revival of colistin. Recently published recommendations suggest use of higher doses than those used previously, although these may be associated with a higher rate of seizures and nephrotoxicity. The question of colistin combination therapy, mainly carbapenem-colistin combinations, arises in the treatment of PNM caused by carbapenem-resistant GNB.

Because of lack of evidence on this issue, we do not use combination therapy routinely for carbapenem-resistant GNB PNM, unless meropenem MIC is ≤ 8 μg/ml, when we recommend the addition of high-dose meropenem. The new antibiotics covering carbapenem-resistant GNB, combinations with avibactam may prove beneficial, as avibactam seems to have better penetration than other beta-lactam inhibitors.

Conflict of interests

The authors declared no conflict of interests.

References

1.Hawkey, P.M., et al., Treatment of infections caused by multidrug-resistant Gram-negative bacteria: report of the British Society for Antimicrobial Chemotherapy/Healthcare Infection Society/British Infection Association Joint Working Party. Journal of Antimicrobial Chemotherapy, 2018. 73(suppl_3): p. iii2-iii78.

2. Sartelli, M., et al., Antimicrobials: a global alliance for optimizing their rational use in intra-abdominal infections (AGORA). World journal of emergency surgery, 2016. 11(1): p. 33.

3. Allegranzi, B. and D. Pittet, Preventing infections acquired during health-care delivery. The Lancet, 2008. 372(9651): p. 1719-1720.

4. Balkhy, H.H., et al., The strategic plan for combating antimicrobial resistance in Gulf Cooperation Council States. Journal of infection and public health, 2016. 9(4): p. 375-385.

5. Laxminarayan, R., et al., Antibiotic resistance—the need for global solutions. The Lancet infectious diseases, 2013. 13(12): p. 1057-1098.

6. Tenover, F.C., Mechanisms of antimicrobial resistance in bacteria. American journal of infection control, 2006. 34(5): p. S3-S10.

7. Sader, H.S., et al., Antimicrobial susceptibility of Gram-negative organisms isolated from patients hospitalized in intensive care units in United States and European hospitals (2009–2011). Diagnostic microbiology and infectious disease, 2014. 78(4): p. 443-448.

8. De Kraker, M.E., et al., Mortality and hospital stay associated with resistant Staphylococcus aureus and Escherichia coli bacteremia: estimating the burden of antibiotic resistance in Europe. PLoS medicine, 2011. 8(10): p. e1001104.

9. MacVane, S.H., Antimicrobial resistance in the intensive care unit: a focus on gram-negative bacterial infections. Journal of intensive care medicine, 2017. 32(1): p. 25-37.

10. Izadpanah, M. and H. Khalili, Antibiotic regimens for treatment of infections due to multidrug-resistant Gram-negative pathogens: An evidence-based literature review. Journal of research in pharmacy practice, 2015. 4(3): p. 105.

11. Edwards, S.J., C.E. Emmas, and H.E. Campbell, Systematic review comparing meropenem with imipenem plus cilastatin in the treatment of severe infections. Current medical research and opinion, 2005. 21(5): p. 785-794.

12. Livermore, D.M., A.M. Sefton, and G.M. Scott, Properties and potential of ertapenem. Journal of Antimicrobial Chemotherapy, 2003. 52(3): p. 331-344.

13. Lapuebla, A., et al., Activity of meropenem combined with RPX7009, a novel β-lactamase inhibitor, against Gram-negative clinical isolates in New York City. Antimicrobial agents and chemotherapy, 2015. 59(8): p. 4856-4860.

14. Lapuebla, A., et al., Activity of imipenem with relebactam against Gram-negative pathogens from New York City. Antimicrobial agents and chemotherapy, 2015. 59(8): p. 5029-5031.

15. Solomkin, J.S., et al., Phase 2, randomized, double-blind study of the efficacy and safety of two dose regimens of eravacycline versus ertapenem for adult community-acquired complicated intra-abdominal infections. Antimicrobial agents and chemotherapy, 2014. 58(4): p. 1847-1854.

16. Sader, H.S., et al., Antimicrobial activity of ceftazidime-avibactam against Gram-negative organisms collected from US medical centers in 2012. Antimicrobial agents and chemotherapy, 2014. 58(3): p. 1684-1692.

17. Scott, L.J., Ceftolozane/tazobactam: a review in complicated intra-abdominal and urinary tract infections. Drugs, 2016. 76(2): p. 231-242.

18. Sader, H.S., et al., Antimicrobial Activities of Aztreonam-Avibactam and Comparator Agents against Contemporary (2016) Clinical Enterobacteriaceae Isolates. Antimicrobial agents and chemotherapy, 2018. 62(1): p. e01856-17.

19. Temkin, E., et al., Ceftazidime-avibactam as salvage therapy for infections caused by carbapenem-resistant organisms. Antimicrobial agents and chemotherapy, 2017. 61(2): p. e01964-16.

20. Hussein, K., et al., Management of post-neurosurgical meningitis: narrative review. Clinical Microbiology and Infection, 2017. 23(9): p. 621-628.

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Table (1): UK hospitals bacterial resistance results (parenteral AB)

MDR GNB	Susceptible to ….	Resistance to….
Acinetobacter baumannii	• Tazobactam / piperacillin • Imipenem / meropenem • quinolones • colistin • aminoglycosides • trimethoprim •	-
Klebsiella spp. Enterobacter spp. Serratia spp. Citrobacter spp	• two or fewer of carbapenems • trimethoprim /colistin. • temocillin • β-lactamase inhibitors • aminoglycosides • piperacillin/tazobactam • tigecycline • quinolones • third-generation cephalosporins •	-
Proteus spp., Morganella spp. Providencia spp.	• Only to carbapenems. • And the new BL/BLI combinations (ceftolozane/tazobactam or ceftazidime/avibactam). • They are resistant to colistin and tigecycline by inherent. •	• Aminoglycosides. • piperacillin/tazobactam • Third-generation cephalosporin.


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