A Case for Caution: Breaking Down Antimicrobial Resistance

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AS ANTIMICROBIAL resistance grows into a global crisis, effective treatment strategies for drug-resistant infections are more essential than ever. Robert Bonomo, Case Western Reserve University School of Medicine, Cleveland, Ohio, recently shared his expert recommendations on navigating these complex cases. Using a real-world example of a young medical student with a highly resistant *Pseudomonas aeruginosa* infection, Bonomo explored key approaches to managing some of the most challenging pathogens encountered in clinical practice today. Bonomo's recommendations offer a roadmap for clinicians facing infections caused by multidrug-resistant organisms, emphasizing tailored, evidence-based strategies for tackling resistant gram-negative pathogens.

A PECULIAR CASE

Bonomo began his talk by describing an interesting real-world case of a 24-year-old medical student who was run over with his own car and sustained burn injuries on his back as a result of being trapped under the manifold. After a few days in the hospital, the medical student developed fever and chills, indicating that the wound had become infected. Blood cultures indicated *P. aeruginosa*, susceptible only to gentamicin. That raises the question for physicians: What is the best course of action in this case?

TREATMENT STRATEGIES IN DIFFERENT PATHOGENS

Bonomo continued describing the most common and problematic gram-negative pathogens physicians are likely to encounter in cases such as this. This included extended-spectrum β-lactamase-producing organisms (ESBL), AmpC β-lactamase (AmpC), carbapenem-resistant *Enterobacteriaceae* (CRE), difficult-to-treat (DTR) *P. aeruginosa*, Carbapenem-Resistant *Acinetobacter baumannii* (CRAb), and *Stenotrophomonas maltophilia* (Steno).

EXTENDED-SPECTRUM β-LACTAMASE

In cases of ESBL infections, ceftriaxone and other cephalosporins are commonly used for infections where ESBL-producing *Enterobacteriaceae* (ESBL-E) are not yet suspected, such as uncomplicated urinary tract infections (UTIs). Uncomplicated cystitis caused by ESBL-E can be effectively managed with nitrofurantoin and trimethoprim-sulfamethoxazole (TMP-SMX), with ciprofloxacin, levofloxacin, and carbapenems serving as alternatives. However, Bomono stressed that the use of these alternatives is discouraged when nitrofurantoin and TMP-SMX are effective, as higher generation antibiotics should be reserved for more severe cases to maintain their effectiveness.

Bonomo's recommendations offer a roadmap for clinicians facing infections caused by multidrug-resistant organisms

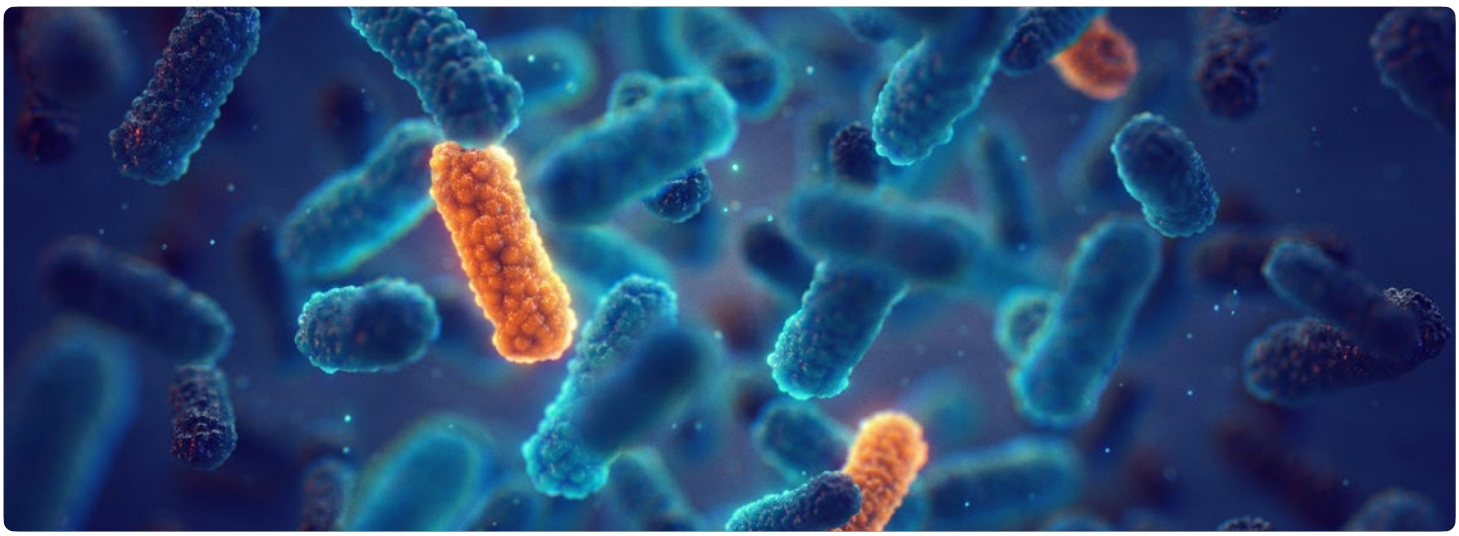
In cases of pyelonephritis and complicated UTIs (cUTIs) caused by ESBL-E, the recommended antibiotics are TMP-SMX, ciprofloxacin, or levofloxacin, while ertapenem, meropenem, and imipenem-cilastatin are preferred when resistance or toxicities preclude the use of TMP-SMX or fluoroquinolones. Bonomo also mentioned that aminoglycosides can be an option for an alternative treatment of pyelonephritis and cUTI; however, it is best to avoid if possible, as in renal infections. These do act well in the kidneys and sterilizing the urine.

For ESBL-E infections outside of the urinary tract, the recommended antibiotics are meropenem, imipenem-cilastatin, or ertapenem. In patients who are critically ill or experiencing hypoalbuminemia, meropenem or imipenem-cilastatin are the preferred carbapenem. Bonomo recommended administering oral TMP-SMX, ciprofloxacin, or levofloxacin after clinical responsiveness, if achieved, provided that the susceptibility to these antibiotic agents is demonstrated.

Additionally, it is recommended that the administration of piperacillin-tazobactum be avoided in ESBL-E infection outside the urinary tract, even if susceptibility to the drug is demonstrated. However, if the drug is initiated as an empiric therapy before the organism is identified as ESBL-E, and the patient demonstrates clinical improvement, no change or extension of antibiotic therapy is necessary.

The avoidance of piperacillin-tazobactum stemmed from the MERINO trial, as Bonomo described, which showed evidence that meropenem is preferable to piperacillin-tazobactam for ESBL infections due to better clinical outcomes.[1] Bonomo also mentioned that cefepanime is not recommended for treatment of ESBL-E infections, pyelonephritis, and complicated UTIs, as ESBLs can break down cefapime. However, similar to piperacillin-tazobactum, if it is administered as empiric therapy, it should not be changed or extended.

Bonomo speculated that the results of this trial will challenge the recommendations that were implemented as a result of the MERINO trial.



On the other hand, Bonomo explained that the PeterPen trial, currently underway in Europe, will make different assumptions about using β-lactamase inhibitors than the MERINO trial. In short, the article by Bitterman et al.[2] reported on the design of the PeterPen trial, where the rationale for further replication of randomized controlled trials was the threefold difference in mortality rates between the two arms in the MERINO trial. Such striking difference was never previously observed in a randomized comparison between antibiotics.[2] Bonomo speculated that the results of this trial will challenge the recommendations that were implemented as a result of the MERINO trial.

AMPC β-LACTAMASE

Moving to AmpC β-lactamase (AmpC), Bomono explained that AmpC-producing organisms, such as the *Enterobacter* species, present unique challenges. He went on to explain why ceftriaxone is not advisable for these infections, as it can induce AmpC production, rendering the drug ineffective. However, cefepime can be an option for strains with lower AmpC production. While carbapenems are safer for higher AmpC production due to their resistance to AmpC enzyme degradation.

CARBAPENEM-RESISTANT *ENTEROBACTERIACEAE*

Moving to CREs, Bomono explained that for infections caused by *Enterobacterales* isolates that exhibit susceptibility to meropenem and imipenem-cilastatin, but are not susceptible to ertapenem, the preferred treatment approach is the use of extended-infusion meropenem, or imipenem-cilastatin, if no carbapenemase gene has been identified.

For UTIs caused by CRE, agents such as nitrofurantoin, TMP-SMX, ciprofloaxin, or levofloaxin are preferred when possible. Additionally, a single dose of an aminoglycoside is an alternative option for uncomplicated cystitis caused by CRE. For more systemic infections, newer agents such as ceftazidime-avibactam and meropenem-vaborbactam are available, with cefiderocol as an additional option in some cases. However, fosfomycin use should be limited to uncomplicated CRE cystitis caused by *Escherichia coli*, as the *fosA* gene can hydrolyze Fosfomycin and may lead to clinical failure.

In cases of pyelonephritis and cUTIs caused by CRE, TMP-SMX, ciprofloxacin, or levofloxacin are the preferred treatment options, as well as ceftazidime-avibactam, meropenem-vaboractam, imipenem-cilastatin-relebactam, and cefiderocol.

MULTIDRUG-RESISTANT AND DIFFICULT-TO-TREAT *PSEUDOMONAS AERUGINOSA*

Bonomo explained that physicians who encounter multidrug-resistant and DTR *P. aeruginosa* should use traditional non-carbapenem β-lactam agents, such as piperacillin-tazovactam, ceftazidime, and cefepime, when susceptibility is demonstrated. In resistant cases, the recommended agents are ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-cilastatin-relebactam, and cefiderocol. These agents are also recommended for pyelonephritis and cUTIs, and infections outside of the urinary tract caused by DTR *P. aeruginosa*.

A PECULIAR CASE: CONTINUED

Circling back to the medical student, molecular analysis revealed bla_{VIM-2}, a gene that encodes the metallo-β-lactamase enzyme, and can break down a wide range of β-lactam antibiotics such as carbapenems. The analysis also revealed resistance to ceftolozane-avibactam, meropenem-vaborbactam, imipenem-cliastain-relebactam, and cefepime-enmerazobactam. However, susceptibility

to cefiderocol was revealed and the patient recovered after a 14-day therapy with cefiderocol and gentamicin.

CARBAPENEM-RESISTANT *ACINETOBACTER*

In discussing CRAb, Bonomo emphasized that cefiderocol has become a key treatment option. However, he cautioned against using cefiderocol as a monotherapy for CRAb infections, advising instead to combine it with another antibiotic to improve effectiveness. This approach, he explained, may help prevent the rapid development of resistance, a significant risk when cefiderocol is used alone against highly resistant strains.

STENOTROPHOMONAS MALTOPHILIA

Turning to Steno, Bonomo noted its inherent resistance to many antibiotics, making it especially challenging to treat. He highlighted TMP-SMX as the standard treatment but acknowledged that some resistant strains might require alternative options. In such cases, high-dose minocycline in combination with TMP-SMX or levofloxacin can be effective. Additionally, he mentioned that the combination of ceftazidime-avibactam and aztreonam could bypass some resistance mechanisms in *Stenotrophomonas*, making it a useful strategy for treating more complicated infections.

The patient recovered after a 14-day therapy with cefiderocol and gentamicin

> **Bonomo stressed the importance of antibiotic stewardship as a cornerstone of modern medicine**

CONCLUSION

In his closing remarks, Bonomo stressed the importance of antibiotic stewardship as a cornerstone of modern medicine. He highlighted that while novel treatments and tailored approaches are essential for combating resistant infections, preserving the effectiveness of existing antibiotics is equally crucial. Thoughtful stewardship, using antibiotics judiciously, and avoiding broad-spectrum agents when narrow-spectrum drugs suffice, help curb the emergence of resistance. Bonomo reminded clinicians that every treatment decision contributes to the global fight against antimicrobial resistance, emphasizing that with careful management, the medical community can continue to protect the efficacy of antibiotics for future generations.

References

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