Fellows Column: A Gut Feeling: Antibiotic Stewardship in the Setting of Multi-Drug Resistant Enterobacteriaceae Neonatal Sepsis

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Abstract:

The role of enteric microbiota in both physiologic and pathologic processes of the human body remains an incompletely understood and rapidly developing field of inquiry. Enterobacter is a genus of gram-negative facultative anaerobes exhibiting widespread resistance to various antibiotic therapies. It belongs to the family Enterobacteriaceae, including such prominent members as Klebsiella, Escherichia, Shigella, and Salmonella. Here we present the case of an infant male on ventilatory support who developed hospital-acquired ventilator-associated pneumonia with cultures positive for multi-drug resistant (MDR) Enterobacter absuriae.

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Identification:

The genus of bacteria now known as *Enterobacter* initially belonged to a grouping known as Aerobacter. In the mid-twentieth century, classifying species such as Aerobacter aerogenes proved difficult as it was nearly indistinguishable from Klebsiella by microbiological techniques. Therefore in 1960, Hormochei et al. proposed that members of the genus *Aerobacter* be divided into the two genera *Enterobacter* and *Klebsiella*. By this classification, members of the genus *Enterobacter* were generally motile and expressed peritrichous flagella, whereas *Klebsiella* were typically nonmotile and non-flagellated (1). However, it should be noted that more recent categorizations based on genetic factors have revealed exceptions to these rules. *Enterobacter cloacae* is considered the nomenspecies of the genus, meaning that all newly identified members of the taxon are classified based on their similarity to *E. cloacae* (2, 3).

To this day, *Enterobacter* and *Klebsiella* often remain grouped in both clinical and phylogenetic classifications. Both genera belong to the family *Enterobacteriaceae,* so named for, including such notable disease-causing genera as *Escherichia*, *Salmonella,* and *Shigella*. Non-pathogenic members of this group include many symbiotic enteric florae. Others exist as saprophytes in the environment, which metabolizes decaying organic matter in the soil, sewage, and vegetation(4). Members of *Enterobacteriaceae* are included in the mnemonic "ESKAPE," signifying *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii Pseudomonas aeruginosa*, and *Enterobacter cloacae* as prevalent nosocomial infections exhibiting antimicrobial resistance (2).

In recent decades, the range of microbiological characteristics used to define Enterobacteriaceae has greatly expanded. When characterized by phenotype, *Enterobacteriaceae* are unpigmented gram-negative bacilli. Metabolically, they are facultative anaerobes that are catalase positive, oxidase negative, non-spore-forming, and non-sulfate-reducing. *Enterobacter* and *Klebsiella* are lysine decarboxylase positive but are ornithine and arginine dihydrolase negative (5).

Restriction fragment length polymorphism (RFLP) with pulse-field gel electrophoresis (PFGE) is the current gold standard of classifying newly identified members of the genus (3, 6). In this technique, the bacterial genome is degraded by incubation with restriction endonucleases specific for known genetic consensus sequences. The resulting fragments are then segregated by length using gel electrophoresis. Other methods which classify bacteria by genotype include polymerase chain reaction (PCR) amplification of enterobacterial repetitive intergenic consensus (ERIC) sequences of repetitive extragenic palindromes (REP). A study compared ERIC and REP genetic sequences against RFLP electrophoresis using the heat shock protein 60 gene (*hsp60*), which is highly conserved among taxon members. The authors concluded that REP PCR was superior to ERIC PCR at identifying clinical isolates based on RFLP standards. However, ERIC PCR could more precisely differentiate between specific genovars (6). The highly conserved 16S rRNA sequences are also available to identify new strains. Commonly isolated strains in humans include *E. cloacae, E. absuriae, E. hormaechei, E. kobei, E. ludwigii,* and *E. nimipressuralis* (7, 8).

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Clinical relevance:

The term "sepsis" is derived from a Greek root meaning "to rot." It denotes a generalized dysregulated host inflammatory response. This typically disseminates from a previously localized infectious trigger and can progress to septic shock, characterized by hypotension and reliance on vasopressors. Sepsis occurring in neonates is broadly categorized based on the timing of onset, with early-onset sepsis occurring within the first seven days of life and late-onset after seven days. While group B streptococci (GBS) is well-recognized as the most prevalent pathogen in neonatal

sepsis, many other infectious agents have been described(9). Early-onset neonatal sepsis is more often associated with GBS, coagulase-negative *staphylococci*, *Escherichia coli*. Late-onset neonatal sepsis exhibits a shift towards *Staphylococcus aureus* and members of the *Enterobacteriaceae family(10)*. Enterobacter accounts for an estimated 22.2% of nosocomial gram-negative bacteremia in one cohort study on neonatal sepsis (11). The current mainstays of empiric treatment include gentamicin, ampicillin or amoxicillin, and third or fourth-generation cephalosporins(10).

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Crucial to septic patient management is the principle of source control, as stated by international guidelines set forth with the Surviving Sepsis Campaign. Source control aims to restrict microbial dissemination from infectious foci and impede pathogenic proliferation therein. This is typically achieved by physical means, including but not limited to incision and drainage for abscess, catheter removal for urinary tract infection (UTI), suctioning for pneumonia, and debridement for soft tissue infection (12).

Neonates are particularly susceptible to nosocomial infections with opportunistic pathogens. In one retrospective cohort study of 230 neonatal intensive care unit (NICU) patients, 15% of late-onset neonatal sepsis was due to enteric gram-negative bacilli (13). Another separate study of 120 culture-confirmed neonatal sepsis patients found that *E. cloacae* accounted for 39.5% of gram-negative bacilli species isolated (14). Delayed development of a diverse intestinal microbiome was associated with sequential growth of *Staphylococcus*, *Enterococcus*, and *Enterobacter* with eventual progression to *Bifidobacterium*, a marker for healthy neonatal microbiota (15).

Pathogenicity and Antimicrobial Resistance:

Like most pathogenic gram-negative bacilli, members of this group produce endotoxin lipopolysaccharide (LPS). Therefore they are capable of inducing gram-negative sepsis and all complications thereof. In particular, the presence of a 2-hydroxymyristic acid moiety on the lipid A substituent is associated with increased neonatal mortality(16). *E. cloacae* is cytotoxic to murine macrophages and simian renal epithelial cells in the presence of 2-mercaptoethanol, a reducer of disulfide bonds. The same authors found that 27% of studied strains expressed a type III secretion system capable of introducing substances into target cells (17).

Interestingly, inoculation of the pea plant (*Pisum savitum*) with the strain *Enterobacter MN17* confers resistance to cadmium. Cadmium is a naturally occurring toxic heavy metal considered a soil pollutant(18). Additionally, human cells have been demonstrated to require divalent metal ion transporters (DMTs) for cadmium intake in vitro(19). Finally, regulation of transition metal ion concentrations via sequestration or decreased activity of DMTs is a known mechanism of the host response to microbial infection (20). Therefore, taken together, these data may represent a series of evolutionary adaptations that allow Enterobacter species to restrict local microbial competition by restricting the availability of limiting nutrients.

The decreased susceptibility to antibiotic therapy characteristic of organisms in the ESKAPE group can be broadly attributed to bacterial adaptations which alter intracellular concentrations of active antimicrobial agents. One mechanism is metabolic degradation of medications by bacterial enzymes, such as extended-spectrum β-lactamases (ESBL). The β-lactamase, AmpC, is an important factor in resistance to cephalosporins in many diverse strains of gram-negative enteric bacteria(21). The *ampC* gene can either be encoded on the bacterial chromosome or on a plasmid, which likely contributes to its far-reaching prevalence across many taxa of microbes. The AmpR repressor protein constitutively represses it(22). Mutations in AmpR and AmpD, an enzyme that recycles peptidoglycan degradation products, result in overexpression of the AmpC cephalosporinase (23). The presence of either ceftazidime or aztreonam selects for mutations in both the *ampD* and *ampR* genes, which confer overexpression and resistance (24).

"Furthermore, Klebsiella and Enterobacter are the two most prevalent producers of the plasmid-encoded carbapenemase blaKPC, and horizontal transfer of these plasmids can be traced across the eastern United States (25). A wide variety of carbapenemases have been described exhibiting serine hydrolase or zinc metalloenzyme activity against drugs such as imipenem and meropenem (26). "

Furthermore, *Klebsiella* and *Enterobacter* are the two most prevalent producers of the plasmid-encoded carbapenemase bla_{KPC}, and horizontal transfer of these plasmids can be traced across the eastern United States (25). A wide variety of carbapenemases have been described exhibiting serine hydrolase or zinc metalloenzyme activity against drugs such as imipenem and meropenem (26). Resistance to imipenem has also been observed in the *E. aerogenes* by regulating the expression of Omp35/Omp36 porin proteins. Notably, this regulation involves both increases and decreases in the presence of proteins in this group, suggesting that this resistance mechanism involved more than a simple efflux of proteins from the cell (27). Similarly, resistance to both fluoroquinolones and aminoglycosides can be conferred by the efflux by the efflux pumps coded by the *qepA* and *rmtB* genes. These were likely transferred to *Enterobacter* via plasmids traced to strains of *Escherichia coli (28)*. Fluoroquinolones differ from β-lactams in that they target the DNA replication machinery of bacteria, exerting antimicrobial effects at the level of the nucleus rather than

the cell wall. Resistance to fluoroquinolones in the *Enterobacteriaceae* family can also be found on the bacterial chromosome in the form of mutations in DNA gyrase, the mechanistic target of fluoroquinolones (29). These data reinforce the need for prudent antibiotic stewardship in the setting of rapidly developing antibiotic resistance.

Case presentation:

We present a case of a 6-week-old preterm, very low birth weight male hospitalized since birth with a history of neonatal respiratory distress and pulmonary edema requiring surfactant administration. This patient had been intubated and remained on long-term ventilatory support. A follow-up chest X-ray revealed a right-upper-lobe opacification that previous studies had not seen. Laboratory studies from the same day revealed a new neutrophilic leukocytosis with left-shift as well as thrombocytopenia. Tracheal aspirates, urine, and blood were sent for culture. In the interim, the patient was started on empiric antimicrobial therapy with intravenous gentamicin and vancomycin for nosocomial pneumonia. The patient exhibited clinical improvement in the day following empiric therapy, possibly due to the synergistic effect of aminoglycosides combined with the gram-negative activity of aminopenicillins.

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Initial cultures of the patient's tracheal aspirate isolated many gram-negative bacilli, identified as *E. cloacae* complex exhibiting multi-drug resistance. At this time, empiric therapy with vancomycin was discontinued, and pathogen-directed therapy was established with cefepime. Gentamicin was continued. Subsequently, further classification of the offending isolates revealed *E. absuriae*. Follow-up sputum cultures were negative for continuing infection.

Discussion:

Fourth-generation cephalosporins, piperacillin-tazobactam, and carbapenems are generally effective treatment for AmpC-producing strains of enteric gram-negative bacilli. However, carbapenems typically should not be considered first-line therapy. They are often considered agents of last resort for clinical use against resistant or refractory infections(26). As stated previously, mechanisms of rising resistance to carbapenems have been demonstrated worldwide. Therefore, the establishment of potential carbapenem-sparing regimens warrants further investigation. Concerning cephalosporins, third and fourth generations may be the treatments of choice for ESBL-producing *Enterobacter*. A multicenter cohort study showed improved outcomes using ceftazidime-avibactam to treat *Enterobacteriaceae* species, including *Enterobacter (30)*. However, it must be noted that widespread resistance to monotherapy with cefotaxime and ceftazidime, both third-generation cephalosporins, has been documented in pediatric populations of California and the mid-western and central United States (31). Cefepime, the only -generation cephalosporin approved in the United States, has well-reported efficacy as a carbapenem-sparing agent in treating these pathogens (32, 33). Third-generation cephalosporins may result in a greater risk of antibiotic resistance than fourth-generation agents (34). It should be noted that these studies with cephalosporins exhibited the greatest efficacy when applied in conjunction with proactive infection source control rather than with antibiotic therapy alone.

Piperacillin-tazobactam has also been shown to be effective in treating bacteria that produce extended-spectrum β-lactamases (ESBL) in vivo (35). Two multicenter, double-blind, randomized placebo-controlled clinical trials demonstrated piperacillin-tazobactam to be non-inferior to meropenem, as well as meropenem-vaborbactam, in treating UTIs and bloodstream infections, respectively, with ESBL-producing *Enterobacteriaceae (36, 37)*. β-lactams will exhibit maximum bactericidal effect when combined with β-lactamase inhibitors such as nacubactam (38). Multiple retrospective cohort studies have also demonstrated the efficacy of piperacillin-tazobactam treatment of ESBL-producing Enterobacteriaceae. These findings are partially attributed to the relatively weak induction on AmpC β-lactamase observed with piperacillin-tazobactam (22). While these data suggest piperacillin-tazobactam to be a suitable carbapenem-sparing agent, care must be taken to forestall increasing resistance to it as well(39).

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Ultimately, decisions regarding the precise antibiotic regimens combat MDR should be guided by local antibiograms reflecting local resistance patterns. Complete elimination of exposure to Enterobacteriaceae family members is not feasible due to their pervasiveness in the environment and the human microbiome. Therefore, identifying antimicrobial agents suited to treat pathology caused by these organisms sustainably is paramount. Here we present the case of an acute onset nosocomial pneumonia with cultures positive for *E. absuriae.* In this patient, cefepime and gentamicin resulted in culture-negative repeat tracheal aspirates.

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