ECHO Antibiotic Stewardship Program: Management of ESBL gram negative bacteremia- the Merino Study

Charles Krasner, M. D.
UNSON
Sierra Nevada Veterans Affairs Med Center
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Sites of antibiotic action - β-lactam antibiotics block bacterial cell wall production leading to cell death.
Gram-positives (*Staph, Strep*) - cell wall on the outside
Gram negatives (*E.coli, Klebsiella, pseudomonas*) - cell wall sandwiched inside 2 membranes
The β lactam antibiotics all have a β lactam ring that allows it to bind to and inactivate the enzymes (referred to as PCN-Binding Proteins) that make the cell wall strong, resulting in cell death.
To block the bacteria- killing effect of the β-lactam class of antibiotics, Bacteria have acquired plasmid mediated enzymes called β-lactamases that open up the β-lactam ring and therefore inactivate the antibiotic.
Some β-lactamase enzymes have a very restricted activity against some older antibiotics, but the serious problem right now is the growing incidence of broadly active (extended spectrum) β-lactamases effective against the most potent antibiotics available.

Chronology of β-lactamases found in Gram negative bacteria

1960s- first plasmid mediated β – lactamase discovered in Greece. Named TEM after the patient (Temoniera)

Soon after TEM-2 discovered, a closely related enzyme as well as SHV

These 3 enzymes are the most common plasmid mediated β-lactamases found in gram-negative bacteria- Enterics, Pseudomonas, H. influenza and N. gonorrheae. Inactivates PCN and narrow spectrum cephalosporins – such as Keflex or cefazolin (1st generation ceph). However – not active versus higher generation, workhorse ceph - ceftriaxone, ceftazidime and cefepime.

Early 1980s- after 3rd generation cefotaxime was introduced, in Germany, France and US, new plasmid mediated β-lactamases were found that broadened their activity to now being able to inactivate all third generation cephalosporins (ESBLs). These were mutated forms of the earlier β-lactamases and have been given names such as TEM-10, TEM-12 and SHV- 5 etc. Other extended spectrum β- lactamases include CTX-M and OXA.

Now- ESBLs, initially seemingly confined to hospital and SNFs, have moved into the community on a broad basis.
Extended Spectrum Beta-lactamases (ESBLs)

- Changes in 1-5 amino acids near active site serine of TEM-1 (or SHV-1) greatly increase activity against 3rd gen cephalosporins and monobactams.
  - TEMs 3-29, SHVs 2-6; still inhibited by clavulanate
  - Carbapenems are only reliable β-lactams vs ESBL producers
  - Mainly seen in *E. coli* and *K. pneumoniae*
  - Located on transferable plasmids that may carry additional resistance genes
EXTENDED SPECTRUM
β-LACTAMASE (ESBL) PRODUCING
ENTEROBACTERIACEAE

THREAT LEVEL
SERIOUS

This bacteria is a serious concern and requires prompt and sustained action to ensure the problem does not grow.

- 26,000 drug-resistant infections
- 1,700 deaths
- 140,000 enterobacteriaceae infections per year

$40,000 in excess medical costs per year for each infection
Appearance of increasingly resistant bacteria, now heralding untreatable superbugs
Right now, options to treat ESBLs include β-lactamase inhibitors. These inhibitors are added to bind to and neutralize the bacteria’s β-lactamase so the antibiotic can kill the bacteria. Tazobactam has in-vitro activity vs. ESBL, and so pipercillin/tazobactam (Zosyn) is often used to treat serious infections—particularly bacteremia – involving ESBL secreting gram negatives.

β-lactam antibiotics

- Penicillins
  - Ampicillin
  - Piperacillin
- Beta-lactam/beta-lactamase inhibitors
  - Ampicillin/sulbactam
  - Amoxicillin/clavulanate
  - Ticarcillin/clavulanate
  - Piperacillin/Tazobactam
How should we best treat these increasingly common and potentially deadly infections by drug resistant bacteria?

• While carbapenems (meropenem, ertapenem) are reliably effective against ESBL secreting gram negatives, the negative drawback to this is the new emergence of carbapenem-resistant (CRE) bacteria - which may be completely untreatable. Washoe already has had a few cases and one death.

• Would be preferred if “carbapenem-sparing” strategies were effective.

• As tazobactam can neutralize the ESBL, some studies have suggested pip/tazobactam (Zosyn) may be a worthwhile alternative choice.

• The MERINO study was therefore specifically developed to answer the question if Zosyn is an equally effective alternative to carbapenem in these cases.
The Merino Study

- “Effect of Piperacillin-Tazobactam vs Meropenem on 30-Day Mortality for Patients With *E. coli* or *Klebsiella pneumoniae* Bloodstream Infection and Ceftriaxone Resistance: A Randomized Clinical Trial”
  
  Harris, PN et al. *JAMA*, 984-90, Sept 11 2018.

International, multi-center study—Canada, Australia, Singapore and 6 other countries, 2014-2017

Non-inferiority study- attempt to show equivalence between these 2 antibiotics in 379 bacteremic patients with documented susceptibility to both drugs. UTIs most common site, followed by intra-abdominal
Study design

• Patients randomized 1:1 to receive either intravenous Zosyn 4.5 grams every 6 hours or meropenem 1 gram every 8 hours for the first 4 days of therapy. After 4 days treating physicians could either stop therapy, adjust therapy as they desired, or continue the study drug up to 14 days.

• Primary efficacy outcome was all-cause mortality at 30 days

• Secondary outcomes looked at adverse events - C.diff, secondary infection, new resistant infection, etc

• Results were as per-protocol

• Study was stopped early as the difference was so great between groups there was no chance this would show “non-inferiority” (i.e. no worse)
Study results

Pip/tazobactam – (23/187)- 12.3% mortality at 30 days

Meropenem- (7/191)- 3.7% mortality at 30 days

Conclusion– Zosyn is not “noninferior” to meropenem in patients with ESBL gram negative bacteremia and “these findings do not support use of Pip-tazobactam in this setting “
Conclusion

- Antibiotic pressure has lead to the selection of broadly active $\beta$-lactamases (ESBLs) that neutralize almost all cephalosporins, the usual workhorse antibiotic for serious gram – negative infections, particularly E. coli and Klebsiella
- Avoiding overuse of carbapenems may delay wide-spread appearance of drug resistant CRE superbugs. One potential “carbapenem sparing” candidate was pip/tazobactam. Question raised was whether or not Zosyn is an acceptable alternative to treat this patients
- However, the Merino study of pip/tazo vs. meropenem for serious, bacteremic infections by ESBL secreting gram negatives showed the marked superiority of meropenem in these cases
- Unfortunate byproduct of increased meropenem use will inevitably lead to the wide-spread appearance of super-resistant bugs and increased death in these patients
- ***Antibiotic Stewardship, particularly avoiding the unnecessary treatment of asymptotic bacteriuria, is crucial to preserve the activity of critical antibiotics***