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October 2023 Critical Care Case of the Month: Multi-Drug Resistant *K. pneumoniae.*

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History of Present Illness:

A 75-year-old man presented from a skilled nursing facility with altered mental status and hypotension. He had a seven-year-long history of steroid-dependent myasthenia gravis, but had previously declined Covid vaccination, and subsequently experienced a severe case of COVID-19 pneumonia five months prior to admission. This resulted in chronic respiratory failure and renal failure for which he subsequently underwent tracheostomy, tunneled subclavian vein dialysis catheter placement and percutaneous endoscopic gastrostomy (PEG). He had resided in a skilled nursing facility since then, requiring four subsequent hospital readmissions for complications. These sequentially included septic shock due to a catheter associated blood stream infection, an intra-abdominal abscess due to PEG migration into the peritoneum resulting in fungal blood stream infection, recurrent intra-abdominal infection with multiple organisms, and bacterial pneumonia. Treatment of these infectious complications included replacement of the tunneled dialysis catheter and exploratory laparotomy with debridement of multiple abscesses. The abdominal wound was left open to heal by secondary intention. The patient received multiple courses of broad-spectrum antibiotics over the preceding four months including (at various times) ampicillin/sulbactam, anidulafungin, piperacillin/tazobactam, cefepime, colistin, meropenem, micafungin, TMP/SMZ, and tobramycin. During his most recent admission three weeks previously, the patient experienced rectal hemorrhage due to ulceration caused by a rectal tube, and a sacral decubitus pressure ulcer was discovered.

Late on the day of admission, staff at the skilled nursing facility where the patient resided noted altered mental status and a BP of 55/38, but reported no other new symptoms. They administered 2L of normal saline, cefepime and vancomycin, and transferred the patient for admission to our ICU at l am. The patient was non-verbal due to delirium and ventilator dependence and could offer no further history. His full code status was described by skilled nursing staff as "adamantly full code."

Physical examination:

- Vital Signs: Temperature: 96.5 F. Heart rate 114 bpm. Respiratory rate 19 bpm. Blood pressure BP 74/36 mmHg (on norepinephrine 50 mcg/min infusion). SpO2 100% (on 30% FiO2).
- The patient was chronically critically-ill appearing and severely deconditioned.

- An 8.0 cuffed tracheostomy, a PEG and a tunneled right subclavian hemodialysis catheter were present– none of which appeared obviously infected.
- HEENT was otherwise unremarkable (ophthalmological examination was not performed).
- The lungs were clear.
- Cardiac exam was tachycardic and hyperdynamic.
- The abdomen had a large midline wound lined with pink, non-odorous granulation tissue. The abdomen was otherwise soft and nontender.
- A 6X6cm sacral pressure wound extended into subcutaneous tissues and was not obviously infected.
- Stools removed from a rectal tube were maroon and heme positive.
- No skin lesions were noted.

Laboratory results:

- CBC: WBCC 24.4 x 10^9/L, Hb 8.3 g/dL, platelets 193 x 10^9/L
- Electrolytes: Na 142 mmol/L, K 3.7 mEq/L mEq/L, Cl 109, bicarb 11 mEq/L,
- Renal function: BUN 94 mg/dL, creatinine 3.5 mg/dL
- Liver Enzymes: AST 1790 U/L, ALT 1111 U/L, Alkaline phosphatase 270 IU/L, albumin 1.8 mg/dL, t-bilirubin 0.7 mg/dL
- Lactate 6.4 mmol/L
- Procalcitonin 12.7 ng/mL
- Random cortisol level was 8.2 mcg/dL.

A chest radiogram is depicted below (Figure 1).

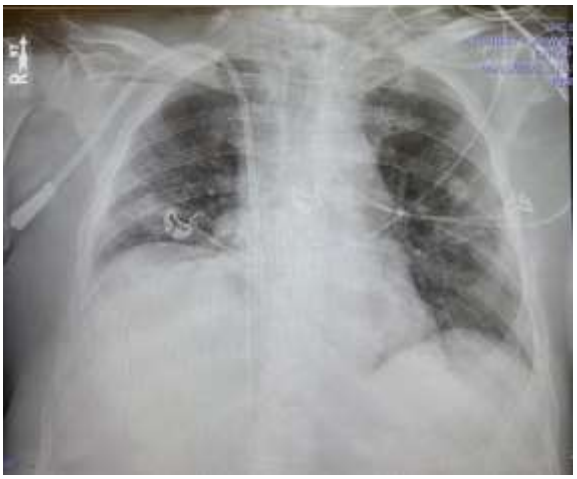

Figure 1. Admission portable chest x-ray.

A presumptive diagnosis of septic shock and adrenal insufficiency were made, and piperacillin/ tazobactam, vancomycin and hydrocortisone were administered intravenously. The patient received an additional 3.5L of normal saline over the following 8 hours; but nevertheless, required increasing doses of intravenous norepinephrine, phenylephrine, vasopressin and epinephrine infusions to maintain MAP >60 mmHg. It is now morning.

Which of the following ***actions are most important*** to be immediately undertaken?

1. The tunneled dialysis catheter should be removed.
2. Computerized tomography of the chest, abdomen and pelvis should be obtained.
3. Prior microbiology results and local antibiograms should be reviewed.
4. Antibiotic coverage should be broadened.
5. Point of Care echocardiography should be performed.

Correct!
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4. Antibiotic coverage should be broadened.
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Options 3,4 and 5 are the most appropriate immediate actions. The most likely diagnosis is septic shock. The patient is at high risk for infection with multi-drug resistant (MDR) organisms and his mortality is greatly increased if the correct antibiotic is not initiated as soon as possible. Risk factors this patient has for infection with MDR organisms include: ICU admission, bedridden status, presence of invasive devices, prior use of broad-spectrum antibiotics, and surgery. It will be difficult to predict the antibiotic sensitivity of the unknown organism, but review of local antibiograms has revealed that amikacin typically has the highest sensitivity rates (>90%) against MDR gram negative bacilli in blood isolates of hospitalized patients. Detailed review of prior culture results should further inform the choice of antibiotics.
Although his hypotension is likely due to septic shock, other causes might be revealed by a point of care echocardiography. Unexpected findings that could change clinical care include LV dysfunction due to unrecognized ischemic heart disease or stress cardiomyopathy and RV dysfunction due to pulmonary embolism. Other unexpected findings could include pneumothorax or right-sided cardiac vegetations (the patient is at risk for endocarditis with prior fungal dialysis catheter infection).
Most clinicians would consider this patient too unstable to safely transfer him for computerized tomography or to have his tunneled catheter removed, although the later remains a consideration and could perhaps be performed at the ICU bedside.
Stress dose steroids should be continued as he is at risk for iatrogenic adrenal insufficiency due to prolonged use of corticosteroids and his random cortisol level is inappropriately low for the level of physiological stress he is experiencing.
Microbiology results from the referring institution were received and reviewed. This revealed the following positive results over the past four months, (all of which were appropriately and apparently successfully treated): a highly resistant *Acinetobacter baumanii* in a BAL specimen (sensitive only to amikacin and ampicillin/sulbactam), *Candida glabrata* in a blood culture and off a central line tip (subsequently removed), and KPC *Klebsiella pneumoniae*, *Mycobacterium abscessus* and *Stenotrophomonas maltophilia* from surgical swabs of the abdomen. Local antibiograms had consistently identified amikacin as the antibiotic with the lowest risk of resistance (<10%) by gram negative bacilli in blood isolates of hospitalized patients over the prior decade.

Which of the following are the ***most important consideration*** in regards to the possible administration of amikacin in this patient?
1. Aminoglycosides are absolutely contraindicated because they can worsen myasthenia gravis
2. Aminoglycosides have unacceptable nephrotoxicity and newer antibiotics such as beta-lactam/beta-lactamase combinations and carbapenems are always preferred.
3. If given, the loading dose of aminoglycosides must be reduced in patients with renal failure.
4. The patient appears to have extremely high mortality risk and is at high risk for infection with MDR organisms.
5. All of the above

Correct!
4. The patient appears to have extremely high mortality risk and is at high risk for infection with MDR organisms.

Although the side effects of aminoglycosides weigh in the decision to administer them, the most immediate threat to this patient's life is septic shock. The antibiotic most likely to cover the organism should be employed unless absolutely contraindicated.
The loading dose of a medication does not depend on its half-life, but rather on its volume of distribution, therefore a loading dose of aminoglycosides should not be reduced in patients with life threatening infections and renal failure. Renal failure will however require lengthening the time between doses. A pharmacy consultation can be helpful in this regard.
A loading dose of 15 mg/kg of amikacin was administered and the antibiotics started on admission continued. Infectious disease consultation was obtained. The consultant did not change the antibiotics (3), but added an order to continue amikacin 8.75 mg/kg every 24 hours with a pharmacy consult to monitor amikacin trough levels and adjust subsequent dosing.
A DNA probe of a blood culture specimen drawn on admission identified *Klebsiella pneumoniae* with CTX-M (ESBL) and NDM-1 (carbapenemase) genes within 27 hours of admission. *Klebsiella pneumoniae* grown out of blood and respiratory secretions, was resistant to all cephalosporin, carbapenem and beta-lactam antibiotics including ceftazidime/avibactam, ceftolozane/tazobactam, and meropenem/vaborbactam, but sensitive to all three aminoglycosides.

Which of following statements is/are ***true***?
1. Genes coding for beta-lactamases and carbapenemases can be shared between bacteria via plasmids.
2. CTX-M and NDM genes are common mechanisms of ESBL and carbapenem resistance respectively in the world, with rapidly increasing prevalence in the United States.
3. Unlike KPC, carbapenem resistance organisms with NDM are typically also resistant to newer beta-lactamase inhibitor combination antibiotics such as ceftazidime/avibactam, ceftolozane/tazobactam, and meropenem/vaborbactam.
4. MRNA Covid vaccines were over 95% effective in preventing serious complications of Covid-19 infection. This patient would likely have been spared 9 months of critical illness ultimately resulting in mortality if he had been properly vaccinated.
5. All of the above

Correct!
5. All of the above

CTX-M comprises a set of 160 related genes that make up the most common type of ESBL in the world, rapidly increasing now in the United States (4). The CTX-M gene naturally resides in the chromosomes of Kluyvera species – non-pathogenic flora of the human gastrointestinal tract that can however transmit the CTX-M gene to pathogenic Enterobacteriaceae via plasmids.
The NDM (New Delhi metallo-beta-lactamase) gene represents a mechanism of carbapenem resistance (5). The resistance is due to a plasmid-mediated carbapenemase that typically also confers resistance to newer beta-lactamase inhibitor combination antibiotics, which are typically efficacious against other mechanisms of carbapenem resistance.
Within 36 hours, the patient was awake and alert, epinephrine, phenylephrine and vasopressin were discontinued, and norepinephrine reduced to 5 mcg/min. The vasopressor was eventually weaned and the patient was transferred to the general medical ward. Eravacycline was later added to his

antibiotic regime once further susceptibility testing resulted. The patient survived a one-month hospitalization and was discharged back to his skilled nursing facility in poor condition. He continued to require recurrent readmissions and died 4 months later with another episode of refractory septic shock caused by the same multi-drug resistant Klebsiella organism (5).

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