Infections in the ICU

Caring for critically ill patients is a costly venture, and this patient population experiences significant morbidity and mortality. One of the largest contributing factors is the high incidence of infections and sepsis in intensive care units (ICUs). In fact, in non-cardiac ICUs 60% of patients will die from infection and related sepsis, accounting for 40% of all ICU expenses. Unfortunately, these numbers continue to increase. A 1992 study, the European Prevalence of Infection in Intensive Care (EPIC), examined the prevalence and epidemiology of infection in 1417 ICUs throughout Western Europe. The subsequent Extended Prevalence of Infection in Intensive Care (EPIC II) attempts to update this information using global data.

The EPIC II was a prospective, multicenter, observational, 1-day point prevalence study. Intensive care units in 75 countries were recruited. All patients present in the ICU on May 8, 2007, from midnight to midnight, were included in the study; demographic, physiological, bacteriological, and therapeutic information, including type of admission (surgical, medical, trauma) and comorbidities, was obtained on case report forms. Simplified Acute Physiology Score II (SAPS II), which measures disease severity, and Sequential Organ Failure Assessment (SOFA) score, which measures degree of organ failure, were documented. In addition, data were requested on each of these patients until time of discharge or 60 days.

A total of 1265 ICUs participated from Western Europe (n=667), Central and South America (n=210), Asia (n=137), Eastern Europe (n=97), North America (n=83), Oceania (n=54), and Africa (n=17). Of these, 94% had continuous physician coverage, 60% were university/academic hospitals, and 66% were mixed medical-surgical units. A total of 13,796 adults were evaluated on the study date; 62% were male, 62% were surgical patients, and 52% had at least 1 comorbidity. Of these, 51% had an infection and 71% were receiving prophylaxis or treatment with antibiotics. Sixteen percent of infected patients were receiving antifungals.

Sites of infection included the respiratory tract (64%), abdomen (20%), bloodstream (15%), renal/urinary tract (14%), skin (7%), catheter-related (5%), and central nervous system (3%). Microbial isolates were obtained in 70% of infected patients; of these 47% were gram-positive, including Staphylococcus (S) aureus (21%) and methicillin-resistant S aureus (MRSA, 10%), S epidermidis (11%), vancomycin-sensitive (7%) and -resistant enterococcus (4%), and Streptococcus pneumoniae (4%). Gram-negative organisms comprised 62% of positive isolates, including Pseudomonas species (20%), Escherichia coli (16%), Klebsiella species (13%), Acinetobacter species (9%), Enterobacter (7%), and extended-spectrum beta-lactamase-producing organisms (2%). Of the remaining positive isolates, 19% were fungal and 5% were anaerobes.

The SAPS II and SOFA scores, the number of comorbidities, and duration of ICU stay before the study day were higher in infected vs. non-infected patients (p<0.001 for all). In fact, the infection rate for a pre-study day ICU stay of 0 or 1 vs. >7 days was 32% vs. 70% (p<0.001). This relationship was especially pronounced with MRSA, S aureus, Acinetobacter, Pseudomonas, and Candida species. Factors that were found to be independently associated with increased infection rates using multivariate logistic regression included: medical admission or admission after emergency surgery or trauma; referral from the hospital floor or other hospital; comorbid chronic obstructive pulmonary disease, cancer, human immunodeficiency virus (HIV) infection, immunosuppression, mechanical ventilation, and renal replacement therapy on the study day, and greater SAPS II scores.

The overall ICU mortality rate was 18.2% (n=2370) and hospital mortality rate was 24.2% (n=3143). The ICU mortality rate among infected vs. non-infected patients was 25.3% vs. 10.7% (p<0.001) and hospital mortality rate
was 33.1% vs. 14.8% (adjusted odds ratio [OR] 1.51, 95% confidence interval [CI] 1.36 to 1.68, p<0.001). In addition, infected patients vs. non-infected patients also experienced longer lengths of stay in the ICU (16 [interquartile range (IQR) 7 to 34] vs. 4 [IQR 1 to 14] days, p<0.001) and in the hospital (29 [IQR 14 to 57] vs. 13 [IQR 7 to 31] days, p<0.001). Factors that were found to be independently associated with increased hospital mortality rates using multivariate logistic regression included: comorbid cancer, heart failure, immunosuppression, cirrhosis, *Pseudomonas*, *Enterococcus*, or *Acinetobacter* species infection, older age, greater disease severity (SAPS II score), and mechanical ventilation or renal replacement therapy on the study day.

The highest infection rates were found in Central and South America (60%), followed by Eastern Europe (56%), Asia (53%), Western Europe (49%), North America (48%), Oceania (48%), and Africa (46%). The greatest variation in infecting organism occurred with *Acinetobacter*, with a 4% rate in North America up to 19% in Asia. Infection rates were higher in countries in which health care comprised a lower proportion of the gross domestic product (GDP). For instance, in countries in which <5% of GDP was devoted to health care, the infection rate was 62%; those with 5 to 9% of GDP devoted to health care had a 54% infection rate, and those with >9% of GDP devoted to health care had a 48% infection rate (p<0.001). The rates of ICU and hospital mortality were highest in Central and South American and Eastern European countries and lowest in Oceania.

This study effectively highlights the high prevalence of ICU infections. Previous studies demonstrated an increasing rate of gram-positive or an equal rate of gram-positive and negative infections; however, this study found a larger number of gram-negative than positive isolates. Despite this, the types of infecting organisms were reflective of previous study findings. The authors make note of the fact that infection rates may be affected by local infection control measures. For example, the water supply in some hospitals may contain *Acinetobacter*, and avoiding the use of tap water to flush nasogastric tubes is a simple infection control measure. The high rate of ICU infections noted in this study brings attention to the fact that opportunities exist for implementing infection control measures in this area. In addition, local data should guide empiric antibiotic choices.

This study was in agreement with past analyses that demonstrated a relationship between mortality and the prevalence of infection. The length of time patients were in the ICU prior to the study date was also positively correlated with infection rates, especially those due to MRSA and *Acinetobacter*, *Pseudomonas*, and *Candida* species. Global differences were also observed. Overall and infection-related mortality was lowest in Oceania, possibly as a result of different patient characteristics. One type of bias identified by the authors was lead-time bias, wherein some countries admit patients to the ICU sooner than others. It is also known that ICU services vary considerably in North American and Europe with respect to admission volume and number of beds. Another interesting facet of this study was the inverse link between health care spending as a portion of GDP and infection rates, with more infections in countries with lower expenditures. Some reasons for this were hypothesized to be differences in national antimicrobial policies and antibiotic availability, infection control practices, accessibility and utilization of vaccines, and public health educational efforts directed at infection prevention. The study was unable to determine the proportion of the GDP spent on only ICU patients.

Although this study did an excellent job of capturing global ICU infection rates, comparisons between regions are not straightforward due to variations between health care systems, ICU services, and infectious disease management practices and policies. These differences can be examined to determine their effect on ICU infection rates. A prevalence study, by nature, includes a large number of patients and requires limited data; however, this also means that the amount of patients with long-term illnesses, including sepsis, may be misconstrued. Other disadvantages or biases could include the fact that participation was voluntary, the number of university hospitals was large, data monitoring was not performed, and infection rates may be subject to seasonal variations.

An accompanying editorial compares the results of EPIC with the current EPIC II study. In particular, the incidence of infection in ICU patients is cause for concern, especially in light of efforts in recent years, which underscore the importance of infection control in this setting. The prevalence of infections in ICU patients in EPIC was 45%, while in EPIC II this number had increased to 51%. Similarly, the proportion of patients receiving antimicrobials increased from 62% to 71%. Another cause for concern is the increase in gram-negative infections from 39% to 63% of infections, a number that now exceeds gram-positive infections. The editorialists make note of the increasing levels of resistance to gram-negatives and the concurrent decrease in treatment options. Infections caused by *S aureus* and MRSA declined from 30% to 20% and 60% to 50%, respectively. However, in North America, *S aureus* causes the most ICU infections and MRSA isolates comprise the majority. The prevalence of fungal infections increased from 17% to 19%. Viral infections were rare; however, they are predicted to become more of an issue considering the worldwide pandemic influenza A (H1N1).

Antibiotic resistance continues to be a problem in the ICU. It is known that underlying diseases and treatment interventions in this setting place patients at risk for colonization and infection (i.e., indwelling catheters, immunosuppressants). Clinicians often face a dilemma, since quality care indicators require them to initiate antibiotics early on and doing so will reduce mortality from severe infections; however, it may also spur resistance. Differentiating between colonization and early infection is often problematic. Antimicrobial resistance is likely to continue increasing, even in the
community. In fact, many infections in ICU patients are caused by organisms in and on the patient at the time of arrival, rather than from environmental contamination or cross-contamination from health care workers. Stringent antimicrobial stewardship efforts are critical in the ICU setting.

In conclusion, the EPIC II study draws attention to the fact that infections in critically ill patients continue to be a large problem worldwide. Despite concerted efforts directed at infection control, infections in the ICU appear to be on the rise. Infection rates are positively correlated with mortality and duration of ICU stay and inversely related to health care expenditures as a portion of GDP. Examination of regional differences may provide useful information in optimizing infection prevention and treatment.

Use of Contraindicated Medications in Dialysis Patients Undergoing PCI

Medication errors, including adverse drug reactions, kill over 100,000 patients every year. These are due in part to inappropriate drug prescribing or administration. Dialysis patients are particularly at risk of experiencing such errors due to the renal elimination of many medications. This patient population is expected to grow in number to over 2 million worldwide in the next year.

Percutaneous coronary intervention (PCI) is the treatment of choice for coronary artery disease. Over 1 million of these catheter-based procedures are performed every year. Briefly, a catheter is threaded through the femoral artery up to the aorta and coronary arteries. A coronary angiogram is used to visualize coronary artery stenosis and identify target lesions. A guidewire is passed through the area of stenosis and a small balloon is inflated and/or a stent deployed, breaking up the atherosclerotic plaque that is occluding the vessel, thereby reestablishing blood flow. Serious complications are rare; PCI has been associated with a mortality rate of <0.3% for elective procedures and 1% to 1.5% with more complex patients.

Medications that affect the coagulation cascade are used extensively during the procedure. The day before the planned PCI, patients are initiated on aspirin 325 mg daily. Just prior to the procedure or at its conclusion, patients are given clopidogrel 300 to 600 mg or more. Patients undergoing PCI are anticoagulated with low molecular weight heparin (i.e., enoxaparin), unfractionated heparin, or a direct thrombin inhibitor (i.e., bivalirudin); a glycoprotein (GP) IIb/IIIa inhibitor (i.e., eptifibatide, abciximab) may also be given. After the 60- to 90-minute procedure antithrombin therapy is no longer needed; however, the GP IIb/IIIa inhibitor may be infused for up to 18 hours. Patients are then discharged on dual antiplatelet therapy.

Patients with renal failure on dialysis pose a challenge for clinicians, since several antithrombotic agents are either not recommended or are contraindicated for use in this population. For example, because eptifibatide and enoxaparin are renally eliminated, they are not recommended for use in dialysis patients due to the increased risk of bleeding complications. Abciximab and unfractionated heparin would be safer alternatives, since they are not cleared by the kidneys.

The current study was undertaken to determine the proportion of dialysis patients undergoing PCI that received enoxaparin and/or eptifibatide and their clinical outcomes. Data were obtained from the National Cardiovascular Data Registry (NCDR) CathPCI registry, a database containing patient, hospital, and outcomes information for PCIs from over 800 U.S. sites. Inclusion criteria were dialysis patients treated with at least 1 antithrombotic for PCI; however, those receiving warfarin, argatroban, lepirudin, thrombolytics, dalteparin, and nadroprin were excluded to make the groups more homogenous. A total of 22,778 patients were included; 5084 (22.3%) who received the contraindicated antithrombotics (enoxaparin and/or eptifibatide) and 17,694 that received non-contraindicated antithrombotics (unfractionated heparin, bivalirudin, or abciximab). The primary outcomes were all-cause in-hospital death and in-hospital major bleeding, defined as bleeding requiring a transfusion, prolonging the hospital stay, causing at least a 3 mg/dL drop in hemoglobin, or occurring at 1 or more of the following sites: percutaneous entry, retroperitoneum, gastrointestinal (GI), genitourinary, or other/unknown. Multivariate analysis with adjustment for confounders was used to assess the association between contraindicated antithrombotics and the primary outcomes. In addition, a propensity score for contraindicated antithrombotics was developed wherein the difference in major bleeding or mortality was examined in 5079 matched pairs with similar baseline characteristics.

The cohort on contraindicated antithrombotics included 2375 (46.7%) on enoxaparin, 3261 (64.1%) on eptifibatide, and 552 (10.9%) on both. Characteristics more common in patients receiving a contraindicated antithrombotic were: heart failure, lung disease, active tobacco use; presentation with acute coronary syndrome (ACS), and treated at private or community centers with lower PCI volumes. Characteristics more common in patients who did not receive a contrained antithrombotic included: non-Caucasian, diabetes, PCI history, and cared for at urban centers with training programs and higher PCI volumes.

Among all patients, in-hospital major bleeding and death occurred in 805 (3.6%) and 963 (4.5%) patients, respectively. The most common site of major bleeding in patients on a contraindicated antithrombotic was GI, which occurred in 39.64% vs. 26.10% of patients not on a contrained antithrombotic (p<0.001). The most common site of major bleeding in patients not on a contrained antithrombotic was percutaneous entry site, which occurred in 36.00% vs. 25.36% of patients on a contrained antithrombotic (p=0.002). The primary cause of in-hospital death was cardiac in patients receiving and not receiving a contrained antithrombotic (63.1% vs. 65.1%, p=0.4). The rate of major bleeding was 5.6% in patients on a contrained antithrombotic vs. 2.9% in those not on a
contraindicated antithrombolic (OR 1.93, 95% CI 1.66 to 2.23). Similarly, the rate of death was 6.5% in patients on a contraindicated antithrombolic vs. 3.9% in those not on a contraindicated antithrombolic (OR 1.68, 95% CI 1.46 to 1.95). These differences persisted after multivariable regression analysis (major bleeding, OR 1.66, 95% CI 1.43 to 1.92; death, OR 1.24, 95% CI 1.04 to 1.48).

Among the matched pairs, in-hospital major bleeding was higher in patients on a contraindicated antithrombolic (OR 1.63, 95% CI 1.35 to 1.98) but in-hospital mortality rates were similar (OR 1.15, 95% CI 0.97 to 1.36). In-hospital bleeding was more common in patients on enoxaparin vs. heparin or bivalirudin (5.0% vs. 3.9% and 3.0%, respectively, p<0.001); mortality followed a similar pattern (6.0% vs. 5.4% and 3.0%, p<0.001). This significant association persisted after risk adjustment when compared with unfractiotherapy (major bleeding, OR 1.28, 95% CI 1.04 to 1.59 and death, OR 1.35, 95% CI 1.06 to 1.72) and bivalirudin (death only, OR 1.44, 95% CI 1.11 to 1.88). No significant association was found between eptifibatide and major bleeding or death, before or after adjustment.

In patients with ACS, an increased risk of in-hospital major bleeding was associated with contraindicated antithrombolic use among this entire subset (adjusted OR 1.82, 95% CI 1.52 to 2.17), with enoxaparin vs. unfractionated heparin (adjusted OR 1.28, 95% CI 1.01 to 1.62), and eptifibatide vs. abciximab (adjusted OR 1.39, 95% CI 1.04 to 1.85). Similar associations were found for the risk of death with contraindicated antithrombolic use (adjusted OR 1.20, 95% CI 1.00 to 1.46), enoxaparin vs. unfractionated heparin (adjusted OR 1.36, 95% CI 1.05 to 1.74), and enoxaparin vs. bivalirudin (adjusted OR 1.51, 95% CI 1.15 to 1.98).

In conclusion, over one fifth of dialysis patients who underwent PCI received a medication that was not recommended for use, including enoxaparin and/or eptifibatide. Unfortunately, this was associated with an increased risk of in-hospital major bleeding and death, both in the overall population and in the strata with ACS. It should be noted that the retrospective nature of the study limits the ability to draw conclusions of causality. Despite known risks and labeling to the contrary, these medications are frequently used inappropriately resulting in negative outcomes. The authors hypothesized reasons for use of these agents, including enoxaparin's ease of administration compared to heparin and therefore its inclusion on preprinted ACS order sets; eptifibatide's lower cost compared to abciximab making it the principle GP IIb/IIIa for PCI; and the lack of data regarding use in dialysis. Therefore, the current labeling appears to be appropriate concerning the use of these agents in dialysis patients, particularly in light of the fact that safer alternatives exist. This information provides the opportunity to implement and improve educational efforts directed at medication safety in dialysis patients, including modification of clinical order sets to include a provision for this population.

Medication-Associated Falls in the Elderly

Falls can be extremely dangerous in the elderly, leading to serious complications and even death. Nearly one third of individuals over age 65 fall every year. Falls account for 85% of all injury-related hospital admissions and >40% of nursing home admissions and cost billions annually. The risks of falling and subsequent fractures are increased with the use of certain medications in the elderly. In addition, the number of medications taken by elderly patients continues to increase. Two meta-analyses that previously examined the association between falls in the elderly and use of different medications were recently updated with a third meta-analysis.

The earlier meta-analyses calculated a pooled OR and 95% CI for the risk of falls with the use of psychotropics, neuroleptics, sedatives/hypnotics, antidepressants (particularly tricyclic agents), and benzodiazepines (short- and long-acting). These ORs demonstrated a significant relationship between medication use and falls, and were unaffected when stratified by number of falls, age, percentage of fallers, or residence. Similarly, a pooled OR was calculated for a variety of cardiac medications, with digoxin, type IA antiarrhythmics, and diuretic use found to be weakly associated with falls in elderly patients. Analgesics, including narcotics, non-narcotics, nonsteroidal anti-inflammatory drugs (NSAIDs), and aspirin were not significantly associated with an increased risk of falls, even after stratification by age and percentage of fallers. However, the risk of recurrent falls increased in patients on more than 3 or 4 medications of any class.

In the third meta-analysis, a literature search identified studies that examined the association between medication use and falls in individuals over age 60 years; randomized controlled, case-control, cohort, and cross-sectional studies presenting original data were included. Medication and falls ascertainment was defined as “good” if medications were ascertained when falls occurred and falls were documented prospectively, and “poor” if defined in any other manner. Data collection included OR of exposure and 95% CI, study type and setting, participants' ages, and time and method of fall ascertainment. Pooled OR estimates were updated with Bayesian methodology which incorporated previous information, permitting an OR estimate with a 95% credible interval (CrI), which is the Bayesian equivalent to the CI.

A total of 22 articles were included in the meta-analysis; 10 were cohort (8 prospective), 5 were case-control, and 7 were cross-sectional studies. Nine studies defined a fall similar to the Prevention of Falls Network Europe (ProFaNE) group (an unexpected event in which participants come to rest on the ground, floor, or lower level), while 3 studies used the Kellogg Working Group definition, which excludes falls that are “a consequence of sustaining a violent blow, loss of consciousness, sudden onset of paralysis as in a stroke, or an epileptic seizure.” Medication and falls...
The included studies focused on 9 different drug classes: antihypertensives, diuretics, beta-blockers, sedatives/hypnotics, neuroleptics/antipsychotics, antidepressants, benzodiazepines, narcotic analgesics, and NSAIDs. The Bayesian pooled estimates of OR (95% CrI) for the effect of various medications on the risk of falling are depicted below. The outcome was the occurrence of at least 1 fall.

- Antidepressants: 1.68 (1.47 to 1.91)
- Neuroleptics/antipsychotics: 1.59 (1.37 to 1.83)
- Benzodiazepines: 1.57 (1.43 to 1.72)
- Sedatives/hypnotics: 1.47 (1.35 to 1.62)
- Antihypertensives: 1.24 (1.01 to 1.50)
- NSAIDs: 1.21 (1.01 to 1.44)
- Diuretics: 1.07 (1.01 to 1.14)
- Beta-blockers: 1.01 (0.86 to 1.17)
- Narcotics: 0.96 (0.78 to 1.18)

Antidepressants were most strongly associated with falls, with a pooled OR estimate of 1.68 (95% CrI 1.47 to 1.91). Estimates paralleled the results of the previous meta-analyses, with the exception of beta-blockers, which was updated from a previous OR estimate of 0.93 (95% CI 0.77 to 1.11) to 1.01 (95% CrI 0.86 to 1.17); p=0.05 for the difference between the ORs.

The OR estimates remained relatively unchanged when stratified by setting, percentage of fallers, age, prospective vs. retrospective medications and falls ascertainment, or study design. Studies with good ascertainment of medications and falls demonstrated an increased risk of falls with sedatives/hypnotics, neuroleptics/antipsychotics, antidepressants, benzodiazepines, and NSAIDs. Some studies adjusted ORs for age, sex, comorbidities, disability, cognition, previous falls, and other medications. Using these, the updated Bayesian OR for diuretics was 0.99 (95% CrI 0.78 to 1.25), for neuroleptics/antipsychotics was 1.39 (95% CrI 0.94 to 2.00), for antidepressants was 1.36 (95% CrI 1.13 to 1.76), and for benzodiazepines was 1.41 (95% CrI 1.20 to 1.71).

The current meta-analysis updated previous findings regarding the risk of falls in the elderly with 9 classes of medications. Unlike the results of prior studies, a significant association was no longer found with beta-blockers. Psychotropic medications continued to be associated with an increased risk of falls, including sedatives/hypnotics, antidepressants, and benzodiazepines. Neuroleptics/antipsychotics as well as diuretics were associated with falls prior to adjustment for covariates only. Antihypertensives and NSAIDs also appeared to pose an increased risk of falls in the elderly.

Confounding by indication should be taken into consideration when examining the study results, since the indications for the drugs under study may themselves increase the risk of falls in elderly patients (i.e., arrhythmias, insomnia, neuromuscular and joint disorders). The included studies frequently adjusted for potential confounders using multivariable modeling and reported adjusted ORs. The meta-analysis found little effect of confounding, as the unadjusted ORs were not unlike the pooled adjusted ORs. In addition, the studies added since the prior meta-analyses included a larger number and a higher proportion of patients taking psychotropic medications, with the exception of sedatives/hypnotics.

The authors point out that the Bayesian methodology permitted integration of prior analyses with current data, which strengthened their analysis. One limitation encountered was the small number of studies fit for inclusion; however, those that were included contained a large number of patients. Also, 16 studies were considered to have poor ascertainment of medication and falls. Nevertheless, the current meta-analysis underscores the need for careful consideration when administering medications from these 9 classes to elderly patients.

The Beer’s criteria are a widely-accepted list of medications and medication classes considered potentially inappropriate for use in older adults. Some of these include narcotic analgesics such as propoxyphene and pentazocine, which may lead to central nervous system (CNS) adverse effects of confusion and hallucinations. Certain NSAIDS such as indomethacin may also lead to CNS adverse effects and ketorolac, naproxen, and piroxicam may increase the potential for GI bleeding, renal failure, and hypertension. Benzodiazepines carry the risk of increased sensitivity and prolonged sedation in the elderly. Antihypertensives such as methyldopa, reserpine, doxazosin, clonidine, and short-acting nifedipine are potentially inappropriate due to the risk of orthostatic hypotension, depression, and adverse CNS effects. Many neuroleptics and antipsychotics such as thioridazine and mesoridazine can increase the risk of CNS and extrapyramidal reactions, while antidepressants such as daily fluoxetine may lead to excessive CNS stimulation, sleep disturbances, and agitation. The criteria are further expanded when concomitant disease states are taken into consideration.

Studies have demonstrated increased costs and health care utilization with the use of potentially inappropriate medications, while implementation of the Beer’s criteria reduced problems in the elderly population. In fact, the Centers for Medicare & Medicaid Services use the Beer’s criteria for regulation of nursing homes. The Beer’s list contains a large number of medications, many of which are contained within the classes of drugs examined in the current meta-analysis. Taking the Beer’s criteria and updated studies into consideration when making treatment decisions in the elderly population will potentially reduce health care costs and minimize adverse drug events. Proper utilization will improve patient safety, which is a top priority.
P&T Committee Formulary Action

Line extensions
- Dextrose 20% in water, 500ml
- Heparin 1,000 units/500mL (Cath Lab)
- Heparin 2,000 units/1000mL (Cath Lab)
- Polyethylene glycol powder 17gm
- Oxcarbazepine 300mg/5mL oral susp

Deletions
- Isosorbide dinitrate SR tablet
- prochlorperazine syrup
- sodium sulfacetamide 0.1% ophthalmic ointment

Author: Jennifer Banovic, PharmD, BCPS
Editor: Jennifer Banovic, PharmD, BCPS