Indian J Pediatr (2011) 78:176–184
DOI 10.1007/s12098-010-0253-4

SYMPOSIUM ON INFECTIONS OLD AND NEW

Nosocomial Infections and Multidrug-Resistant Bacterial Organisms in the Pediatric Intensive Care Unit

Eric J. McGrath · Basim I. Asmar

Received: 24 September 2010 / Accepted: 27 September 2010 / Published online: 9 October 2010

Abstract Nosocomial infections in Pediatric Intensive Care Units (PICUs) caused by multidrug-resistant bacterial organisms are increasing. This review attempts to report on significant findings in the current literature related to nosocomial infections in PICU settings with an international perspective. The types of nosocomial infections are addressed, including catheter-related bloodstream infections, ventilator-associated pneumonia, urinary tract infections, gastrointestinal infections and post-surgical wound infections. A review of emerging resistant bacterial pathogens includes methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus sp.*, *Clostridium difficile,* extended-spectrum β-lactamase producing Gram-negative organisms, *Klebsiella pneumoniae* carbapenemase-producing strains and multidrug resistant *Acinetobacter baumannii.* Basic and enhanced infection control methods for the management and control of multidrug-resistant organisms are also summarized with an emphasis on prevention.

Keywords Nosocomial infection · PICU · Multidrug resistant · Bacterial · Prevention

E. J. McGrath · B. I. Asmar
The Carmen and Ann Adams Department of Pediatrics, Children's Hospital of Michigan, Wayne State University School of Medicine,
Detroit, USA

E. J. McGrath (✉)
Children's Hospital of Michigan, Division of Infectious Diseases,
3901 Beaubien Boulevard,
Detroit, MI 48201, USA
e-mail: emcgrath@dmc.org

Introduction

Patients in the Pediatric Intensive Care Unit (PICU) are particularly susceptible to nosocomial infections in part due to the use of invasive devices and procedures in this critically ill population [1]. Although serious infection may prompt admission to the PICU, infection may also be a complication after admission has occurred [2]. Multiple sources have documented that the incidence of nosocomial infections due to antibiotic-resistant organisms is increasing, with specific examples in the Pediatric Intensive Care Unit (PICU) [3–6].

The prevalence of hospital-acquired or nosocomial infections in pediatric patients ranges from 6 to 12% in the PICU and 10 to 25% in the NICU [1, 7–12]. Using a national point prevalence study in US hospitals, *Banerjee et al* calculated the nosocomial infection prevalence to be 3.7 to 25.0 cases per 100 patients for PICUs and 2.7 to 23.8 cases per 100 patients for NICUs, with average prevalence rate of 14 cases per 100 patients in both settings [1].

Certain risk factors have been associated with nosocomial infections due to resistant organisms have been identified. In adult patients underlying disease and severity of illness, inter-institutional transfer of patients, prolonged hospitalization, gastrointestinal surgery and transplantation, as well as exposure to invasive devices of all types, and exposure to prior antimicrobials have been associated with nosocomial infection due to methicillin-resistant *Staphyloccocus aureus* (MRSA), vancomycin-resistant enterococcus (VRE), Gram-negative bacilli, *Clostridium difficile* (*C. difficile*) and *Candida* [13]. Another study of risk factors in adults for infection with carbapenem-resistant *A. baumannii* in the ICU setting showed that transfusion and colonization density (greater proportion of body parts colonized) increased the risk of infection with that organism

[14]. Risk factors for acquiring nosocomial infections due to resistant organisms in PICU patients included patients with transplants and those with underlying lung disease [3].

Outcomes in patients infected with drug-resistant organisms including mortality, length of hospital stay and costs have been investigated [3, 14, 15]. In a review of several studies, Cosgrove showed that there is an association between development of antimicrobial resistance in several organisms and increase in mortality, length of hospital stay, and cost of health care. Inadequate or delayed therapy and underlying disease were thought to be primarily responsible for the adverse outcomes associated with antimicrobial-resistant infections. Higher healthcare costs of $6,000 to $30,000 were found in those patients with resistant organism infections as compared to those with infections due to susceptible organisms [15].

In the study by *Foglia et al.*, PICU patients in St. Louis, Missouri with infections caused by resistant-organisms had greater length of PICU stay and higher crude mortality rates. Patients with resistant Gram-positive infections had greater mean length of hospital and PICU stays after diagnosis than those with susceptible Gram-positive organisms, though the difference did not reach statistical significance. Patients infected with resistant Gram-negative organisms did have significantly greater PICU stay than those infected with susceptible organisms [3].

Types of Nosocomial Infections

Catheter-Related Blood Stream Infections

Catheter-related blood stream infections (CR-BSIs) represent the most common nosocomial infection in pediatric patients [8, 16]. These infections are associated with patient morbidity, mortality and increased hospital costs [16–18]. The most recent National Healthcare Safety Network (NHSN) data from 71 pediatric medical and surgical critical care units from the US demonstrate a pooled mean of 2.9 BSI per 1000 catheter-days with a median of 2.1 BSIs per 1000 catheter-days and interquartile range of 0.0 to 3.8 BSIs per 1000 catheters days [19].

Risk factors for development of CR-BSI have been recognized in PICU patients [18, 20, 21]. Extracorporeal life support, presence of multiple intravascular devices, and longer duration of intravascular device use were associated with an increase in rate and risk of developing CR-BSI in PICU patients [18]. Use of arterial catheter and packed red blood cell transfusion, as well as the presence of a genetic syndrome, were identified by multivariate analysis as risk factors for nosocomial primary blood stream infection (BSI) in PICU patients [20]. Another study reported different risk factors for nosocomial infection: utilization of parenteral nutrition and antimicrobial therapy were independently associated with nosocomial infections in the PICU setting, though not specifically BSIs [22].

In a 2-year prospective study, *Eldward and Fraser* recently reported on the most common pathogens identified as the cause of nosocomial primary blood stream infections in a PICU. Coagulase-negative *Staphylococcus* was the most common (42 of 124 patients), followed by *Enterococcus sp., Candida sp*., *Serratia marcescens, S. aureus, Pseudomonas aeruginosa, , Enterobacter* sp., *Klebsiella pneumoniae, Escherichia coli, Acinetobacter lwoffi, Micrococcus sp., and Bacillus sp.* [20]. Other studies have also shown coagulase-negative *Staphylococcus* as the most common pathogen causing CR-BSI [21, 23, 24].

A number of recent studies reported BSIs caused by resistant organisms, beyond US borders. A recent (2007) 3-year survey study from Israel showed that one-third of BSI *S. aureus* isolates were methicillin-resistant (MRSA) and 30% of their *K. pneumoniae* isolates produced extended-spectrum beta-lactamases (ESBLs) [23]. Another study from India in 2008, reveals that over the period 1994 through 2003, multiple nosocomial blood BSIs were caused by isolates with increasing levels of resistance. For example, one third to one half of their Gram-negative isolates were resistant to all aminoglycosides. Also many Gram-negative isolates had a high degree of resistance to piperacillin-tazobactam and ticarcillin-clavulanate. The most common Gram-negative organisms isolated were *K. pneumoniae*, followed by *Enterobacter sp.* and *Acinetobacter sp.* Among Gram-positive organisms causing BSI in this study, *S. aureus* was the most common isolate. One-third to one-half of all of the *S. aureus* isolates was noted to be MRSA over the duration of the study. In light of these findings, the authors' choice for empiric antimicrobial coverage was vancomycin and carbapenem [6].

Empiric therapy for CR-BSI should consist of an agent to cover Gram-positive and an agent to cover Gram-negative organisms, based on local antimicrobial resistance patterns [16]. The 2009 IDSA Guidelines for Intravascular Catheter-Related Infection provides an extensive review of the management of CR-BSIs in adult and pediatric populations. Vancomycin is recommended for empiric Gram-positive therapy in health care settings with known high rates of MRSA [25]. However, in institutions where *S. aureus* isolates have vancomycin minimum inhibitory concentration (MIC) values above 2 μg/ml, daptomycin or other agents have been recommended for adult patients due to concerns of treatment failures of infections due to MRSA with MIC values of 2 μg/ml [25, 26]. It is not clear from the current literature if pediatric patients have more frequent treatment failures of MRSA infections with MIC values above 2 μg/ml. Linezolid is specifically not recommended for patients with suspected or proven CR-BSI [25].

Daptomycin is not currently Food and Drug Administration (FDA) approved in the US for pediatric patients.

Empiric coverage for Gram-negative bacilli should be based on local susceptibility patterns and the severity of disease. Fourth-generation cephalosporins, carbapenems, or β-lactam/β-lactamase combinations are recommended because of their coverage of *Pseudomonas sp.* An aminoglycoside may also be added empirically, and is specifically recommended for neutropenic patients, those who are severely ill and those with sepsis, in addition to patients known to be colonized with multi-drug resistant Gram-negative organisms. Patient with femoral lines are recommended to have Gram-positive, Gram-negative coverage and well as coverage for *Candida sp.* Culture results should be used to de-escalate antimicrobial therapy when known [25].

The duration of antimicrobial therapy for CR-BSI vary by host and pathogen. CR-BSI management is pediatrics is complex and may diverge from practices in adults due to the pediatric patient's limited vascular access sites and often critical illness in the PICU setting [16]. In most cases, it is recommended that catheters that are infected be removed and that the patient receive intravenous antimicrobial therapy for 7 to 14 days, depending on the isolated pathogen. Duration of therapy is based on the day of the first negative blood culture result. A longer duration of therapy is recommended for CR-BSI caused by *S. aureus*. Even longer durations of antimicrobial therapy are recommended for patients with persistent bacteremia or fungemia due to suppurative thrombophlebitis, endocarditis, osteomyelitis or other severe infections. Coagulase-negative *Staphylococcus sp.* (CONS) may be treated from 5 to 7 days after catheter removal [25].

The process of catheter removal is not always feasible in pediatric patients for the reasons noted above. Antibiotic lock therapy (Vancomycin, Ceftazidime, Cefazolin, Gentamycin, Ciprofloxacin, Ampicillin) may be utilized for infected catheters in combination with systemic antimicrobial therapy if catheters salvage is desired. Ethanol lock therapy is a newer alternative to antibiotic locks for infected catheters, but the IDSA guidelines do not presently recommend this modality secondary to lack of sufficient data to support its use [25].

Ventilator-Associated Pneumonia (VAP)

VAP is diagnosed based on criteria from the US Centers for Disease Control and prevention (CDC) [27]. However, there is no gold standard for the diagnosis of VAP in children or adults. In general, VAP criteria include a new or progressive radiographic infiltrate, consolidation, cavitation or pneumatoceles (in infants under 12 months of age) that has persisted for at least 2 days as well as two of the following: a temperature above 38.5°C or below 35.0°C, a leukocyte count above 10,000/mm3 or less than 5,000/mm3, purulent sputum, or isolation of pathogenic bacteria for endotracheal tube (ETT) aspirates [27]. Age criteria for those infants under 1 year and children greater than 1 year but less than 12 years of age have also been created [28. Specimens obtained from the lower airway for respiratory culture are preferred. The use of bronchoalveolar lavage (BAL), non-bronchoscopic-BAL or protected specimen brush samples are safe and aid in the acquisition of an adequate of sample for respiratory culture in suspected pediatric VAP patients. An excellent review of VAP in ICU settings was written by Foglia et al. [29].

VAP rates from both medical and surgical PICUs from 50 sites across the United States reported in the recent National Healthcare Safety Network (NHSN) data revealed a pooled mean of 2.1 VAP cases per 1000 ventilator-days with interquartile ranges from 0.0 to 3.2 VAP cases per 1000 ventilator-days [19]. In Foglia et al review, VAP rates were reported in 3 to 10% of ventilated patients in PICUs [29]. The rate of VAP in NICUs ventilated patients ranged from 6.8 to 32.3% which may be a reflection of the patient population and difficulty in making the diagnosis in this group of patients [29, 30].

Although the main contributing factor for VAP development is mechanical ventilation, risk factors for the development of VAP have been studied and include the presence of a genetic syndrome, re-intubation, transport out of the PICU, use of neuromuscular blockade agents, and immunosuppression [31, 32]. Other risk factors for the development of VAP include female gender, post-surgical admission diagnosis, the presence of enteral feedings, and the use of narcotic medications [33]. The association between longer duration of mechanical ventilation and greater risk for the development of VAP has been also noted in neonates. In addition, the endotracheal tube itself may become colonized and serve as a portal for organisms to gain access to the respiratory tract [31].

The use of H_2-blocking agents may allow for enteric bacteria to colonize the upper gastrointestinal tract and may predispose pediatric patients to VAP [31]. Other medications that may contribute to the development of VAP include steroids and Total Parenteral Nutrition (TPN) [32]. Narcotic agents have also been associated with VAP [33].

Organisms causing VAP in ICU settings include a wide variety of pathogens. In a study by *Srinivasan et al*, 58 NICU and PICU patients who were mechanically ventilated for more than 24 h were studied for the development of VAP [28]. The most commonly isolated organisms in VAP patients were Gram-negative organisms including *E. coli, Enterobacter sp., Serratia sp., Pseudomonas sp.* and other Gram-negative organisms. The most common Gram-positive organism was *S. aureus* at 23.1%, with 3 isolates (13%) being methicillin resistant. Of note, 10.3% of

patients with VAP had *Haemophilus influenzae* isolated. Additionally, 38% of their VAP patients had polymicrobial infections. Other reviews of pediatric VAP have found *S. aureus and P. aeruginosa* as the most commonly isolated pathogens [29, 34]. Viral pathogens, such as RSV, have also been recovered in pediatric patients with VAP [31].

No guidelines exist for the empiric treatment of VAP in pediatrics, but according to Foglia et al., VAP is the most common reason for the initiation of empirical antibiotics in PICU patients [29]. The patient's underlying disease, prior antimicrobial therapy, mental status (regarding aspiration risk), length of hospitalization, and results of respiratory aspirate Gram-stain results as well as knowledge of local antimicrobial susceptibility patterns should all be considered in the choice of initial therapy [31].

Single agents that may be efficacious for VAP include carbapenems, cefepime, or piperacillin-tazobactam. Fluoroquinolones may also be used for monotherapy for VAP in certain situations, but their use in pediatrics as first line agents is limited due to their association with tendonitis and tendon rupture [35]. Empiric combination therapy for VAP may include those agents noted above in addition to Gram-positive coverage with vancomycin or linezolid therapy [29]. Daptomycin is not routinely recommended as treatment for pneumonia as it breaks down in the presence of lung surfactant [36]. Close attention must be paid to final culture results when available to appropriately de-escalate antimicrobial therapy or discontinue therapy.

There is no specific recommendation for VAP treatment duration of therapy. Short treatment courses of 5 to 7 days may be appropriate in those patients with uncomplicated disease [31], but longer treatment courses may be warranted for critically ill children infected with MDR organisms (MDROs).

Urinary Tract Infections (UTI)

Urinary tract infections in the PICU setting are commonly caused by bladder catheterization. Urinary catheter-associated UTI rates from both medical and surgical PICUs from 37 sites across the United States reported from the National Healthcare Safety Network (NHSN) data revealed a pooled mean of 5.0 UTI cases per 1000 urinary catheter-days with interquartile ranges from 0.0 to 6.6 UTI cases per 1000 urinary catheter-days [19]. Urinary catheters may not play a significant role in neonatal UTI which may be more related to vesico-ureteral reflux in this population [30, 37].

The most common complication of the use of bladder catheterization is infection. Cystitis, pyelonephritis and secondary BSI can occur from catheter-associated UTI. The most commonly isolated pathogens are enteric Gram-negative organisms as well as other perineal flora including *Enterococcus sp.* and *Candida sp.* Patients may or may not have pyuria. Urine from a catheter is considered infected if organism colony counts are greater than 100,000 cfu/ml. The basic management of catheter-associated UTI is the removal of the catheter, when possible. Patients with complications of UTI such as pyelonephritis or BSI require systemic antimicrobial therapy; however, those patients with cystitis alone may clear the infection by simply removing the catheter, potentially obviating the need for systemic treatment. Prior receipt of antibiotics may put the patient at risk for urinary catheter-associated UTI with a resistant organism. Currently, there is no consensus on duration of therapy for urinary catheter-associated UTI [38].

Other Nosocomial Infections

Hospital-acquired gastrointestinal infections can occur with pathogens known to cause illness in the general population including rotavirus, norovirus, adenovirus, enterovirus and astrovirus. Rotavirus outbreaks have been reported in ICU settings, primarily neonatal nurseries [30, 31]. *C. difficile* is an other known GI pathogen that may be hospital acquired, and some studies rank it as the most common cause of nosocomial infectious diarrhea [31, 39]. However, community acquired *C. difficile* infections are increasingly common in pediatric patients. Syndromes associated with infection range from asymptomatic carriage, to watery diarrhea to pseudomembranous colitis. Diarrhea is associated with liquid stools with mucus and blood, and fecal leukocytes. Pseudomembranous colitis associated with *C. difficile* infection may result in systemic symptoms including fever, elevated leukocyte counts, hypoalbuminemia, colonic wall thickening, and other pathologic changes on endoscopy. Colonic mucosa often contains 2–5 mm, raised yellowish plaques. Disease is caused by the actions of toxins A and B produced by the pathogen. *C. difficile* is acquired from the environment or from the stool of other colonized or infected people. Risk factors for acquisition include prolonged hospitalization or having an infected hospital room mate. Risk factors for developing disease include antimicrobial therapy, underlying bowel disease, gastrointestinal surgery and renal insufficiency. Primary treatment of *C. difficile* associated infections is discontinuation of the precipitating antimicrobial therapy in addition to supportive care. Metronidazole taken by mouth for ten (10) days is the first line treatment agent. Oral vancomycin may also be used but should be reserved for those with severe illness or who have not responded to metronidazole therapy [40].

Surgical site infections range from surgical site skin wound infections to the development of mediatstinitis and sternal osteomyelitis after open heart surgery. Infection is a major complication of orthopedic hardware which includes prosthetic joints, pins, nails, rods and other fixation devices.

Infections of vascular graft and patch material, prosthetic valves, and pacemakers, as well as ventricular assist devices may also become infected post-operatively. Peritoneal catheters are known to become infected and may lead to secondary peritonitis. Ventriculo-peritoneal shunts (VPS) and ventriculo-atrial shunts as well as lumbo-peritoneal shunts may all become infected and may lead to shunt malfunction, ventriculitis and other symptoms associated with increased intracranial pressure. Central nervous system shunt catheters may also lead to secondary peritonitis or BSI with the potential to cause endocarditis, depending on the tract and outlet location of the distal portion of the catheter. General treatment principles for surgical wound infections include source control with surgical drainage of localized infections, obtaining intra-operative cultures, and the use of appropriate antimicrobial therapy that is culture result-directed. In device-related infections, surgical removal of the infected device may be necessary to control the infection, i.e. VPS externalization, in addition to the use of systemic antimicrobial therapy [31, 38].

Emerging Resistance

Gram-Positive Pathogens: MRSA, VRSA, VRE and *C. difficile*

S. aureus: MRSA and VRSA

Resistance to methicillin in *S. aureus* is caused by a change in the penicillin binding protein 2a (PBP2a) leading to a low affinity to all β-lactams. The gene causing this change is MEC-A which is carried on a mobile genetic element called staphylococcal cassette chromosome (SCC). Hospital acquired (HA) and Community acquired (CA) MRSA are the result of different MEC-A types. Most HA-MRSA carry MEC-A types I, II, or III and most CA-MRSA, types IV or V. The HA-MRSA is associated with resistance to multiple classes of antibiotics and is carried on a large SCC that puts the organism at a selective environmental disadvantage. However, CA-MRSA is associated with resistance to all β-lactams but only a few other classes of antibiotics. Because CA-MRSA has a small SCC, it does not put the organism at a selective disadvantage and it can, therefore, survive in the community. CA-MRSA is also more likely to carry the genes for a cytotoxin known as Panton Valentine Leukocydin (PVL) which has been associated with skin and soft tissue infections in some patients [41].

Any S. *aureus* isolate, whether methicillin resistant or susceptible, may have inducible clindamycin resistance in the presence of erythromycin resistance. This resistance must be tested for in the laboratory by a D-test and is the result of an inducible methylase encoded by erythromycin ribosomal methylase (*erm*) genes that prevent access to the ribosomal binding site for macrolides, lincosamides (clindamycin) and streptogramin B. In some strains, the *erm* mRNA is not active without the presence of a macrolide, such as erythromycin [41].

Vancomycin resistance has also emerged in *S. aureus*. The vanA ligase gene, from E*nterococcus sp.*, was found in the first completely vancomycin resistant strains of *S. aureus* likely from co-infection/colonization with VRE. These genes are located on transposons which are transferable by plasmids or can be found on mobile chromosomal elements. These resistance mechanisms may be lost by the organism in the absence of vancomycin exposure. The effect that heteroresistance has on MRSA and VRSA in regards to treatment failures in pediatrics patients is yet to be defined [41]. To our knowledge, no VRSA strains have been isolated in pediatric patients to date.

In a recent review article by Creel et al., 11 previously healthy pediatric patients diagnosed with CA-MRSA infections requiring PICU care were reviewed. The small series had a mortality rate of 27%. Mean length of stay (LOS) in these patients was nearly 15 days compared to the average PICU LOS of 2.4 days. Ten of the eleven patients were treated with vancomycin therapy on admission to the PICU, but took a mean of nearly 6 days to sterilize their blood cultures. Six patients had bilateral necrotizing pneumonia and required mechanical ventilation. Nearly all of the patients received combination therapy active against MRSA with vancomycin along with rifampin, gentamicin, clindamycin, and linezolid [42]. It is clear from this review that the optimal strategies for the treatment of MRSA in pediatrics are still yet to be elucidated but may include increased vancomycin dosages in empiric therapy, careful monitoring of serum vancomycin trough levels, monitoring for vancomycin toxicity if higher levels are utilized, and the consideration of combination therapy for severely ill or treatment-refractory patients [26, 42].

Vancomycin Resistant Enterococcus (VRE)

Resistance of *Enterococcus sp.* to vancomycin has been shown to be related to the van genes, noted above. The proportion of enterococcal infections attributed to VRE is approaching 30%. Resistance has been described for both *E. faecalis* and *E. faecium* and is more common in *E. faecium.* High level resistance is plasmid-mediated and can be transferred through conjugation. The vanA gene encodes an inducible protein that leads to the creation of a D-alanine:D-lactate ester rather than the normal D-alanine:D-alanine linkage of the cell wall. Vancomycin binds less avidly to this altered linkage and therefore does not disrupt the cell wall production in these organisms leaving it ineffective [43].

Many enterococci are completely resistant to penicillins and all cephalosporins. *E. faecium* is resistant to all carbapenems, though *E. faecalis* may have varying susceptibility to imipenem, despite resistance to meropenem and ertopenem. For vancomycin resistant strains, treatment with linezolid or daptomycin my be considered. Quinupristin-dalfopristin (Synercid) is not active against *E. faecalis* but is active against *E. faecium* [43].

C. difficile Infection

A hypervirulent strain of *C. difficile*, identified as the North American pulse-field gel electophoresis type 1 (NAP1), has emerged and is responsible for the increasing severity of *C. difficile* infection in the US, Canada, and Europe. Colitis caused by this strain has led to an increase in the number of urgent colectomies. The NAP1 strain overproduces toxin A and toxin B in levels up to 20-fold higher than non-NAP1 strains, and it also produces other toxins [39].

Stopping concomitant antibiotics in ICU patients may not be feasible. As noted above, metronidazole and vancomycin are recommended therapies [39, 40]. However, there is some evidence that oral vancomycin may lead to improved clinical outcomes in those with severe disease. In addition, severely ill patients with ileus may require intravenous metronidazole with oral or intracolonic vancomycin. Other strategies for treatment of *C. difficile* infection include probiotic therapy and intravenous immunoglobulin, but the evidence for these modalities is not strong. Toxin binding agents, such as cholestyramine, may actually bind with intraluminal vancomycin and lead to decreased stool concentrations of this medication and are not currently strongly recommended for therapy. Finally, there is general agreement that anti-peristaltic medications should be avoided with *C. difficile* infection, but, of note also, required sedation medications may have side-effects that slow gut motility [39].

Gram-Negative Pathogens: ESBLs, KPCs, and MDR *A. baumannii*

Extended-Spectrum β-lactamases (ESBLs)

There is no consensus on a precise definition of ESBL-producing organisms. ESBLs, generally, are β-lactamases that can confer bacterial resistance to penicillins, first-, second-, and third-generation cephalosporins, and aztreonam by hydolysis of these antibiotics. These β-lactamases are inhibited by clavulanic acid. Cephamycins, such as cefoxitin, and carbapenems (imipenem, Meropenem) commonly remain effective against ESBLs in most definitions. An extensive review of ESBLs was published in 2005 by *Paterson and Bonomo* [44].

ESBLs derived from TEM-1, TEM-2 and SHV-1 only differ, in some cases, by as few as one amino acid from their basic plasmid-mediated β-lactamase type. However, these small changes result in a tremendous change in the enzyme activity in ESBL-producing organisms and the gained ability to hydrolyze an expansive spectrum of antibiotics, as noted above. The fact that these ESBL producers are inhibited by clavulanic acid separates them from the AmpC-type B-lactamases commonly found in *Enterobacter sp*. which are not inhibited by clavulanic acid. Cefepime, a fourth-generation cephalosporin, may remain effective at treating AmpC-producing organisms, but is not considered as useful against ESBL-producing organisms [44].

Another group of B-lactamases includes the CTX-M group of enzymes. These ESBLs are named for their ability to hydrolyze cefotaxime. These isolates are resistant to cefotaxime, but may also be resistant to ceftazidime despite initially reported MICs in the susceptible range. CTX-M-type ESBLs also hydrolyze cefepime and make the organism resistant to that antibiotic as well [44].

In a recent study 35790 gram-negative aerobic isolates recovered from intensive care units in the North America, *K. pneumoniae* isolates were resistant to third-generation cephalosporins an average of 13%. Over the study period from 1994 to 2000, the percentage of isolates that were susceptible to third-generation cephalosporins fell by 3% [45]. Some ICUs have had third-generation cephalosporin resistance rates above 25% for *K. pneumoniae* [44]. Of note, community-acquired ESBLs have been reported across the globe now, and may infect previously healthy persons without prior medical history [46].

Klebsiella pneumoniae Carbapenemases (KPCs)

Carbapenem-resistant *Enterobacteriaceae* (CRE) have recently emerged as important infectious agents in the health-care setting. Infections with these organisms have been associated with high rates of morbidity and mortality, especially among the critically ill, immunocompromised, those with prolonged hospitalization, and those exposed to invasive procedures [47, 48]. In a report from Israel in 2008 both adults and pediatric patients were identified as being infected with KPC-producing organisms. Of concern in that report were the 5 patients who developed imipenem-resistant strains had prior clinical isolation of imipenem-susceptible strains of *Enterobacter sp*. [48].

The mechanism of resistance is the organism's production of a carbapenemase enzyme, bla_{kpc}. The gene encoding this enzyme is carried on a transposon (mobile piece of genetic material) that increases the risk for dissemination. The rapid detection of these organisms is paramount because appropriate antimicrobial therapies may be drastically different from traditional empiric therapies. Tradition-

al MIC detection methods may show these organisms to have limited to intermediate susceptibility to carbapenems but specific testing, with the modified Hodge test, reveals true carbapenem resistance [47]. KPC-producing organisms are resistant to penicillins, aztreonam, cephalosporins, carbapenems, and many aminoglycosides and fluoroquinolones. Although the KPC-type β-lactamases are inhibited by clavulanic acid and tazobactam, some have acquired other resistance mechanisms making them resistant to these inhibitors and β-lactamase/inhibitor combinations [41, 49].

As treatment options for KPC producing isolates are extremely limited, enhanced infection control practices, namely strict contact precautions, are very important for the control of the spread of these pathogens when they are identified in health-care settings. Active surveillance screening of patients with epidemiologic links to the source patient is recommended [47].

MDR A. baumannii

Global data reveal that antimicrobial resistance among *A. baumannii* species is increasing [50]. Multidrug-resistant *A. baumannii* presently is emerging as a common hospital- and community- acquired infection that is difficult to treat [51]. It is a very resistant and aggressive organism that infects patients with weakened defenses like ICU patients and those with invasive devices. It survives on wet and dry surfaces for long periods [51]. This organism has multiple mechanisms for resistance including an impermeable outer membrane, AmpC β-lactamases, class D OXA-type and class B metallo-β-lactamases which allow the organism to resist carbapenems, porin channels alterations as well as efflux pumps, and other genetic changes that may lead to resistance to fluoroquinolones [52]. Species of *A. baumannii* that were resistant to all known commercially available antibiotics have been described [53].

As a result of the emergence of MDR *A. baumannii*, the use of older antimicrobial therapies, such as intravenous colistimethate (colistin) as well as combination therapies have been employed in critically ill children and adults [54–56]. Synergy between colistin and rifampin has been previously reported in colistin-susceptible *A. baumannii* strains [57]. Favorable clinical outcomes were reported with the use of this combination in adult patients with nosocomial pneumonia, bacteremia and meningitis, although some of the patients received colistimethate in an aerosolized form [56].

The recommended colistin dose in most references is 2.5–5 mg/kg/day divided into 2 or 4 doses [54, 58]. Patients with cystic fibrosis have had higher colistin dosages utilized in their therapies [59, 60]. Current published literature raises a concern for the standard dose's ability to achieve adequate serum drug levels above the pathogen MIC for killing of the organism [59]. The required adjustment for renal insufficiency with this medication also may require further study [55].

Outbreaks: Management and Control

Many of the MDR organisms described above have been implicated in outbreaks or clusters of cases in ICU settings [4, 61–64]. Standard and enhanced infection control methods have been implemented in many ICUs where MDR organisms have been isolated. Standard infection control practices include: basic hand hygiene before and after unit entry with appropriate antimicrobial soaps; aseptic technique when performing invasive procedures; the use of gown, gloves, and mask for sterile procedures; routine environmental cleaning and disinfection; and antibiotic stewardship [52, 63].

Enhanced infection control practices include active surveillance (non-clinical) cultures of patients, staff, and the environment of care, to detect asymptomatic carriage at a single time or repeated at regular intervals; geographic (spatial) cohorting of patients; geographic cohorting of staff; contact precautions (donning gown and gloves at entry of patient care area); dedicated patient equipment (i.e., glucometers and stethoscopes); un-identified unit observations of infection control practices; staff education; and regular consultation with infectious disease specialists [5, 47, 52, 63]. In many reported outbreaks, utilizing these basic practices allowed for the control of the outbreak without unit closure, even in the case of organisms that were multidrug resistant. Additionally, in some centers, the use of periodic screening surveillance cultures has been recommended to better detect potentially unrecognized sources or reservoirs of resistant pathogens in the PICU [4, 5].

Conclusions

The clinician's best strategy to manage nosocomial infections in the PICU setting caused by MDR organisms is to prevent infection or colonization with these organisms in the first place. Although ideal, complete prevention may be an unreasonable goal in light of the potential for "well" patients to be harboring MDROs in the community upon their admission to the PICU. It is likely that a multi-faceted approach to the treatment and management of these organisms when they are identified is needed including strict adherence to enhanced infection control practices, active surveillance cultures of patients, staff and the environment and rapid switch to appropriate antimicrobial therapy upon receipt of the offending pathogen's antimicrobial susceptibility report to better target therapy. Unfor-

tunately, the burden and impact of MDROs in the PICU setting will likely continue to increase.

Future research should focus on the development of novel and safe antimicrobial therapies with activity against MDROs, evidence-based infection control practices and new methods by which MDR pathogens could be rapidly detected before patients enter the PICU setting.

Conflict of Interest None.

Role of Funding Source None.

References

1. Banerjee SN et al. Incidence of pediatric and neonatal intensive care unit-acquired infections. Infect Control Hosp Epidemiol. 2006;27(6):561–70.
2. Toltzis P et al. Meropenem use and colonization by antibiotic-resistant Gram-negative bacilli in a pediatric intensive care unit. Pediatr Crit Care Med. 2009;10(1):49–54.
3. Foglia EE, Fraser VJ, Elward AM. Effect of nosocomial infections due to antibiotic-resistant organisms on length of stay and mortality in the pediatric intensive care unit. Infect Control Hosp Epidemiol. 2007;28(3):299–306.
4. Lin YC et al. An outbreak of methicillin-resistant *Staphylococcus aureus* infection in patients of a pediatric intensive care unit and high carriage rate among health care workers. J Microbiol Immunol Infect. 2007;40(4):325–34.
5. Milstone AM et al. Unrecognized burden of methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant Enterococcus carriage in the pediatric intensive care unit. Infect Control Hosp Epidemiol. 2008;29(12):1174–6.
6. Singhi S et al. Nosocomial bloodstream infection in a pediatric intensive care unit. Indian J Pediatr. 2008;75(1):25–30.
7. Baltimore RS. Neonatal nosocomial infections. Semin Perinatol. 1998;22(1):25–32.
8. Grohskopf LA et al. A national point-prevalence survey of pediatric intensive care unit-acquired infections in the United States. J Pediatr. 2002;140(4):432–8.
9. Herruzo CR, Garcia G, Garcia MP, et al. Nosocomial infection and its impact on the stay in neonatal intensive care unit (1988–1991). Rev Sanid Hig Publica (Madr). 1993;67:153–63.
10. Lodha R et al. Nosocomial infections in pediatric intensive care units. Indian J Pediatr. 2001;68(11):1063–70.
11. Simon A, Bindl L, Kramer MH. Surveillance of nosocomial infections: prospective study in a pediatric intensive care unit. Background, patients and methods. Klin Pädiatr. 2000;212(1):2–9.
12. Sohn AH et al. Prevalence of nosocomial infections in neonatal intensive care unit patients: results from the first national point-prevalence survey. J Pediatr. 2001;139(6):821–7.
13. Safdar N, Maki DG. The commonality of risk factors for nosocomial colonization and infection with antimicrobial-resistant *Staphylococcus aureus*, enterococcus, gram-negative bacilli, *Clostridium difficile*, and *Candida*. Ann Intern Med. 2002;136(11):834–44.
14. Playford EG, Craig JC, Iredell JR. Carbapenem-resistant *Acinetobacter baumannii* in intensive care unit patients: risk factors for acquisition, infection and their consequences. J Hosp Infect. 2007;65(3):204–11.
15. Cosgrove SE. The relationship between antimicrobial resistance and patient outcomes: mortality, length of hospital stay, and health care costs. Clin Infect Dis. 2006;42 Suppl 2:S82–9.
16. Smith MJ. Catheter-related bloodstream infections in children. Am J Infect Control. 2008;36(10):S173 e1-3.
17. Kilgore M, Brossette S. Cost of bloodstream infections. Am J Infect Control. 2008;36(10):S172 e1-3.
18. Odetola FO et al. Nosocomial catheter-related bloodstream infections in a pediatric intensive care unit: risk and rates associated with various intravascular technologies. Pediatr Crit Care Med. 2003;4(4):432–6.
19. Edwards JR et al. National Healthcare Safety Network (NHSN) Report, data summary for 2006 through 2007, issued November 2008. Am J Infect Control. 2008;36(9):609–26.
20. Elward AM, Fraser VJ. Risk factors for nosocomial primary bloodstream infection in pediatric intensive care unit patients: a 2-year prospective cohort study. Infect Control Hosp Epidemiol. 2006;27(6):553–60.
21. Yogaraj JS, Elward AM, Fraser VJ. Rate, risk factors, and outcomes of nosocomial primary bloodstream infection in pediatric intensive care unit patients. Pediatrics. 2002;110(3):481–5.
22. Singh-Naz N et al. Risk factors for nosocomial infection in critically ill children: a prospective cohort study. Crit Care Med. 1996;24(5):875–8.
23. Grisaru-Soen G et al. Nosocomial bloodstream infections in a pediatric intensive care unit: 3-year survey. Med Sci Monit. 2007;13(6):CR251–7.
24. Richards MJ et al. Nosocomial infections in pediatric intensive care units in the United States. National Nosocomial Infections Surveillance System. Pediatrics. 1999;103(4):e39.
25. Mermel LA et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2009;49(1):1–45.
26. Rybak MJ et al. Vancomycin therapeutic guidelines: a summary of consensus recommendations from the infectious diseases Society of America, the American Society of Health-System Pharmacists, and the Society of Infectious Diseases Pharmacists. Clin Infect Dis. 2009;49(3):325–7.
27. Mayhall C. Hospital epidemiology and infection control. 3rd ed. Philadelphia: Lippincott WIlliams & Wilkins; 2004.
28. Services, D.o.H.a.H. 02/13/02 cited; Available from: www.cdc.gov/ncidod/hip/NNIS/members/pneumonia/Final/PneuCriteriaFinal.pdf.
29. Foglia E, Meier MD, Elward A. Ventilator-associated pneumonia in neonatal and pediatric intensive care unit patients. Clin Microbiol Rev. 2007;20(3):409–25. table of contents.
30. Zingg W, Posfay-Barbe KM, Pittet D. Healthcare-associated infections in neonates. Curr Opin Infect Dis. 2008;21(3):228–34.
31. Coffin SE, Zaoutis TE. Healthcare-associated Infections. In: Sarah LP, Long S, Prober CG, editors. Principles and practice of pediatric infectious diseases. Churchill Livingston, an imprint of Elsevier Science; 2008. p. 577–87.
32. Elward AM, Warren DK, Fraser VJ. Ventilator-associated pneumonia in pediatric intensive care unit patients: risk factors and outcomes. Pediatrics. 2002;109(5):758–64.
33. Srinivasan R et al. A prospective study of ventilator-associated pneumonia in children. Pediatrics. 2009;123(4):1108–15.
34. Babcock HM et al. Ventilator-associated pneumonia in a multi-hospital system: differences in microbiology by location. Infect Control Hosp Epidemiol. 2003;24(11):853–8.
35. The use of systemic fluoroquinolones. Pediatrics. 2006;118(3):1287–92.
36. Silverman JA et al. Inhibition of daptomycin by pulmonary surfactant: in vitro modeling and clinical impact. J Infect Dis. 2005;191(12):2149–52.

37. Sastre JB et al. Urinary tract infection in the newborn: clinical and radio imaging studies. Pediatr Nephrol. 2007;22(10):1735–41.
38. Zaoutis TE, Coffin SE. Clinical syndromes of device-associated infections. In: Sarah LP, Long S, Prober CG, editors. Principles and practice of pediatric infectious diseases. Churchill Livingston, an imprint of Elsevier Science; 2008. p. 587–99.
39. Riddle DJ, Dubberke ER. Clostridium difficile infection in the intensive care unit. Infect Dis Clin North Am. 2009;23(3):727–43.
40. Alam S, Mushtaq M. Antibiotic associated diarrhea in children. Indian Pediatr. 2009;46(6):491–6.
41. Miller MB, Gilligan PH. Mechanisms and detection of antimicrobial resistance. In: Sarah LP, Long S, Prober CG, editors. Principles and practice of pediatric infectious diseases. Churchill Livingston, an imprint of Elsevier Science; 2008. p. 1392–403.
42. Creel AM et al. Severe invasive community-associated methicillin-resistant *Staphylococcus aureus* infections in previously healthy children. Pediatr Crit Care Med. 2009;10(3):323–7.
43. Haslam DB, St. Geme JW. Enterococcus species. In: Sarah LP, Long S, Prober CG, editors. Principles and practice of pediatric infectious diseases. Churchill Livingston, an imprint of Elsevier Science; 2009. p. 716–9.
44. Paterson DL, Bonomo RA. Extended-spectrum beta-lactamases: a clinical update. Clin Microbiol Rev. 2005;18(4):657–86.
45. Neuhauser MM et al. Antibiotic resistance among gram-negative bacilli in US intensive care units: implications for fluoroquinolone use. Jama. 2003;289(7):885–8.
46. Doi Y et al. Community-acquired extended-spectrum beta-lactamase producers, United States. Emerg Infect Dis. 2007;13(7):1121–3.
47. Guidance for control of infections with carbapenem-resistant or carbapenemase-producing Enterobacteriaceae in acute care facilities. MMWR Morb Mortal Wkly Rep. 2009;58(10):256–60.
48. Marchaim D et al. Isolation of imipenem-resistant Enterobacter species: emergence of KPC-2 carbapenemase, molecular characterization, epidemiology, and outcomes. Antimicrob Agents Chemother. 2008;52(4):1413–8.
49. Bradford PA et al. Emergence of carbapenem-resistant Klebsiella species possessing the class A carbapenem-hydrolyzing KPC-2 and inhibitor-resistant TEM-30 beta-lactamases in New York City. Clin Infect Dis. 2004;39(1):55–60.
50. Perez F et al. Global challenge of multidrug-resistant *Acinetobacter baumannii*. Antimicrob Agents Chemother. 2007;51 (10):3471–84.
51. Siegel RE. Emerging gram-negative antibiotic resistance: daunting challenges, declining sensitivities, and dire consequences. Respir Care. 2008;53(4):471–9.
52. Maragakis LL, Perl TM. *Acinetobacter baumannii*: epidemiology, antimicrobial resistance, and treatment options. Clin Infect Dis. 2008;46(8):1254–63.
53. Doi Y et al. Extensively drug-resistant *Acinetobacter baumannii*. Emerg Infect Dis. 2009;15(6):980–2.
54. Falagas ME et al. Intravenous colistimethate (colistin) use in critically ill children without cystic fibrosis. Pediatr Infect Dis J. 2009;28(2):123–7.
55. Li J et al. Colistin: the re-emerging antibiotic for multidrug-resistant Gram-negative bacterial infections. Lancet Infect Dis. 2006;6(9):589–601.
56. Motaouakkil S et al. Colistin and rifampicin in the treatment of nosocomial infections from multiresistant *Acinetobacter baumannii*. J Infect. 2006;53(4):274–8.
57. Li J et al. Antibiograms of multidrug-resistant clinical *Acinetobacter baumannii*: promising therapeutic options for treatment of infection with colistin-resistant strains. Clin Infect Dis. 2007;45 (5):594–8.
58. Axline SG, Yaffe SJ, Simon HJ. Clinical pharmacology of antimicrobials in premature infants. II. Ampicillin, methicillin, oxacillin, neomycin, and colistin. Pediatrics. 1967;39(1):97–107.
59. Li J et al. Steady-state pharmacokinetics of intravenous colistin methanesulphonate in patients with cystic fibrosis. J Antimicrob Chemother. 2003;52(6):987–92.
60. Reed MD et al. The pharmacokinetics of colistin in patients with cystic fibrosis. J Clin Pharmacol. 2001;41(6):645–54.
61. Das I et al. Carbapenem-resistant *Acinetobacter* and role of curtains in an outbreak in intensive care units. J Hosp Infect. 2002;50(2):110–4.
62. Ergani-Ozcan A et al. Nosocomial outbreak of vancomycin-resistant Enterococcus faecium in a paediatric unit at a Turkish university hospital. J Antimicrob Chemother. 2008;61(5):1033–9.
63. Simmonds A et al. Outbreak of *Acinetobacter* infection in extremely low birth weight neonates. Pediatr Infect Dis J. 2009;28(3):210–4.
64. Singh N et al. Control of vancomycin-resistant enterococci in the neonatal intensive care unit. Infect Control Hosp Epidemiol. 2005;26(7):646–9.