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Antibiotic Resistance in NICU Pathogens: Mechanisms, Clinical Impact, and Prevention including Antibiotic Stewardship

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Introduction

Antibiotic resistance is a public health crisis. The Institute of Medicine has listed control and reduction of infections caused by antibiotic resistant pathogens in acute care settings as one of the most important issues facing the medical community.[1] The prevalence of antimicrobial resistant pathogens is higher in other intensive care unit (ICU) populations than in the neonatal ICU, but the experience in other populations is useful and can serve to warn NICU providers of the potential future threat. Thus, it is critical to understand the implications of the epidemiology of resistance to craft strategies to reduce antimicrobial resistance (AMR) in the NICU population.

Epidemiology of Antimicrobial Resistant Organisms in the NICU

The epidemiology of pathogens causing hospital-acquired infections in the NICU population is well described, although it should be noted that most of the literature has focused on late onset sepsis. Gram positive pathogens are more common causes of infections than gram negative pathogens and yeast.[2, 3] Staphylococcal species, most notably *S. epidermidis* and *S. aureus*, cause approximately 60–70% of infections. *S. epidermidis* is the most common gram positive pathogen, although many clinical microbiology laboratories do not speciate coagulase negative staphylococci; thus, the epidemiologic picture for other coagulase

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negative staphylococci is incomplete. Gram negative bacilli (GNB) cause approximately 15–20% of infections, most notably late onset sepsis and hospital-acquired pneumonia, including ventilator-associated pneumonia. Finally, *Candida* spp. cause approximately 10% of hospital-acquired infections in the NICU, most often candidemia and catheter-associated blood stream infections.

To date, most of the literature pertaining to antimicrobial resistant pathogens in the NICU reflects single center reports rather than multi-center studies and thus may be skewed toward outbreaks rather than endemic infections.[4–6] Infants hospitalized in NICUs are at risk of developing both colonization and infections caused by antibiotic resistant organisms (AROs). Colonization with resistant organisms has implications for both the colonized infant who can progress to infection and for other hospitalized infants as colonized infants may serve as a reservoir for AROs.[7]

The vast majority of hospital-acquired coagulase negative staphylococci are resistant to oxacillin due to the *mecA* gene as will be described further below. In addition, hospital-acquired coagulase negative staphylococci are multidrug-resistant, e.g., resistant to gentamicin, rifamipn, erythromycin and clindamycin.[8] Thus, treatment options for synergy are limited for this pathogen. *S. warnerii* with higher minimal inhibitory concentrations (MIC) to vancomycin have been described resulting in the concern for “MIC creep”.[9] This concern seems well founded given the frequent use of empiric vancomycin in this population as well as selective pressure resulting from subtherapeutic concentrations of vancomycin at mucosal surfaces and sequestered sites, e.g., biofilms within central venous catheters.

Methicillin-resistant *S. aureus* (MRSA) is a critically important pathogen in the NICU population and has been associated with both endemic and epidemic infections. In addition, the epidemiology of MRSA is changing from being exclusively a hospital-acquired pathogen to a pathogen with widespread distribution in the community capable of causing infection in otherwise healthy individuals. Similarly, the dominant MRSA clones in the NICU have been changing from hospital- to community-associated clones.[6] Reservoirs for MRSA include other colonized infants in the NICU, staff members, the inanimate environment and acquisition from family members, including vertical transmission due to maternal anovaginal colonization in pregnancy.[10] While hospital-acquired strains of MRSA in other patient populations are often multidrug-resistant, strains in the NICU tend to be more susceptible, although it is likely this varies according to local epidemiology and the dominant clone and the type of staphylococcal chromosomal cassette (SCC) present as described further below. Community-associated strains often harbor the virulence factor Panton-Valentine leukocidin and have been found to divide more rapidly than hospital-associated clones. USA300 is now the most common community-associated MRSA clone in the world and has been detected in NICUs.

In the NICU, enterococci are less frequent pathogens than staphylococcal species. Nevertheless, ampicillin-resistant, and more recently, vancomycin-resistant enterococci have been described in the NICU.[11] Fortunately, neither vancomycin-intermediate nor

vancomycin-resistant coagulase negative staphylococci nor *S. aureus* has been described in the NICU population.

Gram negative bacilli are becoming increasingly antibiotic-resistant in healthcare settings and may be occasionally pan-resistant, i.e., resistant to all conventional antibiotics. Fortunately, while pan-resistant pathogens have been rare in the NICU, the increasing threat of multidrug-resistant GNB serves as a warning for close monitoring, infection control, and antibiotic stewardship as will be described further below. In the NICU, the most common resistance patterns noted to date have been resistance to piperacillin-tazobactam, ceftazidime, and/or gentamicin.[12, 13] More worrisome, has been the emergence of extended spectrum β-lactamase producing (ESBL) pathogens that lead to resistance to 3rd generation cephalosporins including cefotaxime, ceftriaxone, and ceftazidime, as well as the monobactam aztreonam.[14] *Klebsiella pneumonia* and *Escherichia coli* are most likely to acquire ESBLs, but these enzymes are also noted in other species.[15] Even more ominous, although not yet prevalent in pediatric populations, are the *K. pneumoniae* carbapenemases (KPCs) that hydrolyze carbapenem agents such as imipenem and meropenem which are the treatment of choice for ESBL-producing pathogens.[16] In fact, some GNB have become resistant to all first-line antibiotics and are only susceptible to polymyxin B and/ or tigecycline, a tetracycline derivative. Interestingly, quinolone resistance and tetracycline resistance are rare among pathogens isolated from patients in the NICU, presumably because these agents are rarely used in the NICU population.[6]

With the advent of fluconazole prophylaxis, aimed at preventing candidemia in very low or extremely low birth weight infants, [17, 18] there has been concern about the emergence of resistance to fluconazole or the emergence of non-*albicans* or non-*parapsilosis Candida spp.* such as has been observed in other populations.[19] During relatively short term clinical trials (6–12 months), fluconazole resistance has not been detected in either infecting or colonizing flora.[17] However, more prolonged follow-up is likely needed to estimate the risk.

Mechanisms of Action and Mechanism of Resistance

Overview

An understanding of the mechanisms of resistance is predicated upon an understanding of the mechanisms of action of antimicrobial agents. Briefly, antibacterial agents can bind to bacterial cell targets and prevent transcription (DNA to RNA), translation (RNA to protein) or interfere with cell wall synthesis as described further in Table 1. Antifungal agents have somewhat different mechanisms of action; amphotericin binds to ergosterol in fungal membranes causing leakage of fungal cell contents.[20] The azoles, including fluconazole, inhibit enzymes involved in ergosterol synthesis. The echiniocandins, which are not used frequently in the NICU, interfere with cell wall synthesis by binding to the protein complex that synthesizes cell wall β-1,3 glucan polysacchrides.

Mechanisms of resistance for both bacteria and yeast are characterized by three major mechanisms (Table 1). These include (i) acquisition of an enzyme that alters the structure of an antibiotic, thereby rendering the agent unable to bind to the target of action; (ii) mutations

in the bacterial target site that prevent antibiotic binding (e.g., mutations in penicillin binding proteins, DNA gyrase, or the proteins involved in ergosterol biosynthesis); or (iii) changes in uptake via multi-drug efflux pumps which remove antibiotics from the microorganism or porins which prevent antibiotic entry into bacterial cells.

Microorganisms are continually mutating; some mutations are silent, some are lethal, and some confer a selective advantage. Bacteria are also avid at acquiring new DNA from other bacteria which may be located on plasmids that often carry multiple resistance genes. Thus, mutations which result in antibiotic resistance are highly desirable from the microorganism's perspective.

The Impact of β-lactamases

As shown in Table 1, β-lactam agents bind to penicillin binding proteins (PBPs) which help to construct new cell wall for dividing bacteria. Gram negative and gram positive bacteria can possess different types of PBPs in varying concentrations. Furthermore, agents differ in their affinity for a given PBP. For example, the broad spectrum carbapenem agents' (with activity against both gram negative and gram positive pathogens) major target of action is PBP 2.

All β-lactam agents (penicillins, cephalosporins, monobactams, and carbapenems) possess β-lactam rings. β-lactamases hydrolyze the ring and alter the configuration of the antibiotic such that the antibiotic can no longer bind to the PBP. There are dozens of β-lactamases with different affinity for different antibiotics. For example, some enzymes preferentially hydrolyze penicillins while others hydrolyze cephalosporins. Such enzymes are inhibited by the β-lactamase inhibitors sulbactam (combined with amipicillin) or tazobactam (combined with ticarcillin). As described above, β-lactamases can hydrolyze 3rd generation cephalopsorins, i.e., the ESBLs, while others can hydrolyze carbapenems, i.e., the KPCs. Some β-lactamases are carried on plasmids which can facilitate transfer to other bacterial cells, while others are located within the chromosome. The nomenclature and spectrum of activity of β-lactamases is complex and has been recently reviewed.[21]

MRSA: Community- vs. Hospital-associated Strains

Resistance to oxacillin in *S. aureus* and coagulase negative staphylococci is due to acquisition of *mecA* which is contained on the Staphylococcal chromosomal cassette (SCC) as recently reviewed.[22] *MecA* is not a β-lactamase, but rather codes for a PBP2 with low affinity for β-lactam agents.[23] Differences in the genetic composition of SCC are the basis for the different phenotypes of community-associated (CA) vs. hospital-associated (HA) MRSA (Table 2). However, the phenotypic distinction between community- vs. hospital-associated strains is gradually blurring as community-associated strains are becoming increasingly resistant.

Resistance to Vancomycin

Thus far, resistance to vancomycin (initially described during the 1990's) has largely been limited to *Enterococcus faecium*, although there are reports of vancomycin resistance in *Enterococcus faecalis.* In fact, *E. faecalis* is more likely to be susceptible to ampicillin as

well. Resistance to vancomycin occurs by two mechanisms: *vanA* or *vanB;* these gene clusters alter the vancomycin target from D-alanine-D-alanine to D-alanine-D-lactate.[24]

Resistance to vancomycin has also been reported in *S. aureus* although the *vanA* and *vanB* gene clusters noted in enterococci have, thus far, rarely been noted in staphylococci. Instead, intermediate vancomycin resistance has been well described which is mediated by alterations in cell wall structure including a thickened capsule and thickened wall which presumably limit vancomycin's access to its D-alanine-D-alanine target.[23] Another phenotype of vancomycin resistance is heteroresistance whereby *in vitro* susceptibility testing of a single strain reveals both susceptible bacterial cells (MIC ≤ 2 μg/ml) and intermediately resistant cells (MIC ≤ 4–8 μg/ml). Heteroresistance can be difficult to detect in the laboratory, but may have clinical implications as described below.

Clinical Impact of Antimicrobial Resistant Pathogens

The mortality and morbidity of AROs may be related to increased virulence, delay in appropriate therapy, and fewer treatment options. Furthermore, antimicrobials required to treat AROs may be less effective, more expensive, or more toxic than conventional therapy. Resistance may be difficult to detect, can cause increased costs and length of stay, and may lead to a vicious cycle of antibiotic overuse, as broader empiric choices are then required. However, attributable mortality to antimicrobial resistance is difficult to measure since critically ill neonates with infections caused by AROs often have comorbid conditions.

Numerous outbreaks of MRSA have been reported in the NICU.[25, 26] MRSA infections typically manifest as skin, eye, and blood stream infections, although other invasive infections can occur.[9, 27–29] In a 7 year retrospective study of 172 *S. aureus* infections occurring in a tertiary care NICU, MSSA caused 123 (72%) and MRSA caused 49 (28%) infections, most commonly, bacteremia and skin and soft tissue infections.[27] The types of infections caused by methicillin-susceptible *Staphylococcus aureus* (MSSA) and MRSA were similar. Although infants with MRSA were younger at presentation, crude mortality was not different. Infected infants exhibited a bimodal weight distribution (potentially due to the large number of full term infants with congenital anomalies cared for at this NICU); 53% of *S. aureus* infections occurred in extremely low birth weight infants < 1000 grams and 27% occurred among term infants with birthweights > 2500 grams, the majority of whom had undergone surgical procedures. Similarly, Cohen-Wolkowiez et al. described a comparable crude mortality rate between infants with MRSA and MSSA blood stream infections, although duration of bacteremia was longer in infants infected with MRSA (4.5 days vs. 1 day, respectively).[30] Management of MRSA in NICUs is further complicated by the complexity of using vancomycin as this agent requires dose adjustment for post-conception age, renal insufficiency, receipt of extracorporeal membrane oxygenation, and body site of infection.[31] Failure to adjust dosing, may lead to low troughs which may lead to treatment failures, particularly for sequestered sites such as the lung or the central nervous system.

As described above, CA- MRSA strains have emerged as a significant cause of infections in the NICU. CA-MRSA strains, like HA-MRSA strains, typically cause skin and soft tissue

infections, although bacteremia, pneumonia, and meningitis, can also occur.[32–34] Although Kuint et al demonstrated that infants with CA-MRSA bacteremia were more premature when compared to infants with HA-MRSA or MSSA bacteremia, mortality rates did not differ.[35]. CA-MRSA infections have caused outbreaks on maternity wards and well baby nurseries, including skin infections among otherwise healthy, full-term newborns, and mastitis and post-partum infections among mothers.[10, 36]

As described above, neonatal bacteremia is most frequently caused by coagulase negative staphylococcal strains with high rates of *mecA* gene carriage. These strains have been found to be harbored by both neonates and staff, suggesting cross- transmission of resistant strains.[37–39] *S. warneri* has been demonstrated to be an important pathogen in the NICU with decreased vancomycin susceptibility as mentioned previously.[40] This observation is particularly concerning since such strains can be shared between neonates and nurse's hands.[9] In one case report, a neonate with 3 weeks of persistently positive blood cultures for *Staphylococcus capitis* was found to be infected with a strain that was heteroresistant to vancomycin.[41] As conventional antibiotic testing may indicate susceptibility, treatment failure (despite removal of central venous catheters) may be due to heteroresistance. Perhaps more concerning, Vilari et al described 81 *S. epidermidis* isolates, including 27 from blood stream infections, most of which demonstrated heterogenous vancomycin susceptibility, although the clinical implications of this was uncertain.[42]

Manifestations of vancomycin-resistant *Enterococcus* (VRE) infection have included bacteremia, meningitis, and endocarditis.[43–47] McNeely et al. reported a significantly greater mean age of onset for VRE bacteremia compared to infections caused by vancomycin-susceptible enterococci, (101 vs. 34 days, respectively). The clinical presentations of VRE vs. susceptible strains were indistinguishable, but infants with VRE bacteremia had significantly higher crude mortality (0/6 vs. 72/94) potentially due to comorbid conditions. Furthermore, conclusions are limited due to the small sample size.[48] Epidemiological investigations following VRE infections have consistently demonstrated a higher ratio of colonized infants compared to infected infants.[49, 50] Thus, a single positive clinical infection may represent a hidden reservoir of colonization.[50] Antibiotic options in VRE infections are limited to bacteriostatic agents, usually linezolid, which have not been been evaluated in large studies in neonatal populations.[43, 44, 50]

Increasing antimicrobial resistance among GNB is of particular concern since many institutions have reported an increased proportion of blood stream infections caused by GNB.[3, 51, 52] Numerous publications from NICUs in both the developed and developing world have described outbreaks of antibiotic resistant gram negative pathogens with well characterized mechanisms of resistance. ESBL-producing *Enterobacter hormaechei* caused five episodes of sepsis in neonates in California over 6 months [53] and ESBL-producing GNB have caused early onset sepsis, suggesting potential maternal colonization in the community. [54] Jeena et al. described a multi-drug resistant *Acinetobacter anitratus* outbreak in a pediatric and neonatal ICU causing 23 infections, primarily post-operative infections and pneumonia, with a 57% mortality rate.[55] Birth weight < 1000 grams and receipt of prolonged antibiotic therapy (>21 days) have been associated with increased risk of infections caused by antibiotic resistant GNB. In developing countries, where GNB cause

a larger proportion of neonatal sepsis than in developed countries, the burdens of resistance are even greater. In a large 10 year study of 6 NICUs in Brazil, Couto et al. demonstrated that 186 (64.1%) of 290 isolates of *K. pneumoniae* were resistant to 3rd generation cephalosporins.[57] Furthermore, it is estimated that 70% of *Klebsiella* spp. blood stream infections in NICUs in developing countries are resistant to gentamicin.[58]

The impact of infection caused by antibiotic resistant GNB has varied. Khasswneh et al. reported a 30% crude mortality rate caused by highly resistant GNB; 48% of deaths occurred within the first 3 days of infection.[59] However, Kristof et al. found no statistically significant difference in mortality between infections caused by ESBL-producing and non-ESBL-producing *Klebsiella* spp. (1/8 vs. 1/37, respectively).[60] Of note, Abdel-hady et al. found that infection with ESBL-producing *K. pneumoniae* was associated with a 3-fold higher crude mortality.[61] Costs attributable to AROs can be remarkable. An outbreak of ESBL-producing *K. pneumoniae* consisting of 8 infected and 14 colonized infants cost nearly $350,000, mainly attributable to increased healthcare worker time and closed hospital beds.[62]

Invasive *Candida* spp. infections are associated with an attributable mortality rate of 13% and are the third most frequent cause of late-onset sepsis in very low birth weight (VLBW) preterm neonates.[3, 63] The burden of resistance is largely determined by the prevalent *Candida* species; *C. albicans* and *C. parapsilosis* species are usually susceptible to fluconazole, while *C. krusei* is intrinsically resistant to fluconazole. Of note, *C. lusitaniae*, a relatively rare cause of candidemia, is intrinsically resistant to amphotericin. While candidemia in adult and pediatric ICUs are increasingly caused by non-albicans species [64–66], this trend has not been noted in NICUs. From 1995–2004, there was no increase in infections caused by *C. glabrata* or *C. krusei* in 128 American NICUs.[63] While there are not data supporting the increased virulence of different *Candida* spp. in NICU populations, speciation is critical to detect possible intrinsic resistance and susceptibility testing should be performed prior to treatment with fluconazole.

Prevention

Judicious Use of Antibiotics

Infants hospitalized in the NICU have high rates of antibiotic use. In a national point prevalence study of 29 NICUs in the United States, 43% of NICU patients were receiving antimicrobials on the survey date.[67] Exposure to antibiotics is a risk factor for AROs; use of penicillin class agents have been associated with emergence of MRSA [68] and in the NICU, use of 3rd generation cephalosporin agents have been associated with the emergence of ESBL GNBs as well as invasive candidiasis.[69, 70]

Antimicrobial stewardship is increasingly being promoted as a means to limit antimicrobial resistance and improve quality of care. The Infectious Disease Society of America reviewed potential strategies to improve antimicrobial use and developed evidence-based recommendations for antimicrobial stewardship programs.[71] One of the hallmarks of successful antimicrobial stewardship programs has been the use of an interdisciplinary team. Such programs report the collaborative efforts of intensivists, infectious diseases physicians,

nurses, pharmacists, hospital epidemiologists, and bioinformatics specialists. However, antimicrobial stewardship programs are not commonly employed in pediatric settings.[72]

The Centers for Disease Control and Prevention (CDC) has initiated a new program to combat the threat of antibiotic resistance in acute care settings. (Arjun Srinivasan, MD, Atlanta, GA, personal communication, March 2010). Called the 'Get Smart in Healthcare Settings: Know When Antibiotics Work' Campaign, it consists of 4 major concepts: timely antibiotic management; appropriate selection, administration, and de-escalation of antibiotics; access to infectious disease expertise; and improved data monitoring and transparency.

Although none of the evidence-based national antibiotic stewardship initiatives have been specifically developed for hospitalized infants, the general principles intended to improve antibiotic use are still applicable to the NICU population as shown in Table 3. Further support that these principles are relevant are provided in studies of biomarkers; IL-8 and CRP have been successfully used to guide initiation of antibiotic therapy [73, 74] and procalcitonin has been used to guide duration of therapy.[75] Appropriate management of suspected infections can be improved by educational interventions stressing adequate blood culture volumes.[76] In the NICU, education about antibiotic spectra of activity may improve antibiotic use as failure to de-escalate antibiotic coverage was often responsible for excessive antibiotic use.[77]

Interventions to improve antibiotic stewardship that use antibiotic restriction have been evaluated in neonatal populations. Restricting the use of cephalosporin agents was associated with a reduction in colonization with multi-drug resistant GNB.[78] Decreasing vancomycin use was considered an important factor in controlling an outbreak of VRE.[49] In contrast, Toltzis et al. compared monthly rotations of gentamicin, piperacillin-tazobactam, and ceftazidime versus unrestricted physician choice for treatment of suspected neonatal sepsis and found no reduction in antimicrobial resistance, hospital-acquired infections, or mortality, although there was notable contamination between the groups.[79]

Another strategy with the potential to increase AROs is the prophylactic use of antimicrobial agents. As mentioned, the prophylactic use of fluconazole has not been associated, thus far, with the emergence of resistance.[17] In a meta analysis of systemic prophylactic vancomycin (either as continuous low dose infusion or intermittent therapy), the authors concluded that there were insufficient data to ascertain the risks of developing antibiotic resistant organisms.[80] In a later study, prophylactic vancomycin-heparin lock reduced the incidence of central line associated blood stream infections in high-risk neonates with long-term central catheters and was not associated with increased vancomycin resistance.[81] While the risk of developing vancomycin resistance may be lower with locks, due to low serum concentrations, larger, multi-center studies are needed to ascertain the long term risks of this strategy.

Infection Control Strategies

As described above, acquisition of AROs can occur via selective pressure from antibiotics or from a reservoir harboring resistant pathogens. Potential reservoirs have been described for

both gram negative pathogens as well as MRSA. These include: other infected or colonized infants in the NICU whose pathogens are transmitted via the hands of healthcare workers; colonized healthcare workers, vertical transmission or post-natal transmission from mothers, post-natal transmission from other family members, the contaminated healthcare environment, intrinsically (contaminated during manufacturer) or extrinsically (contaminated during preparation) infusates or parenteral nutrition.[82]

Numerous studies have addressed risk factors, some of which are modifiable, for infections caused by AROs. Risk factors for infections caused by MRSA have included low birth weight, kangaroo care, eye discharge, and MRSA colonization in an individual infant as well as overall MRSA colonization rate in the NICU.[83, 84] Risk factors for ESBL-producing *K. pneumoniae* infection have included mechanical ventilation; very low birth weight < 1500 grams; parenteral nutrition, and previous treatment with 3rd generation cephalosporins.[61, 85]

Infection control strategies aimed at preventing acquisition and transmission are outlined in Table 4. In addition to education, accurate identification and surveillance for AROs are crucial. Clinical microbiology laboratories must have adequate resources for appropriate susceptibility testing and rapid notification of results. The Department of Infection Prevention and Control must have a surveillance plan in place which includes strategies for outbreak investigations. Surveillance cultures for AROs should be implemented when epidemiologically indicated or if mandated by public health authorities. There are several strategies for targeted surveillance cultures as described in Table 4. Rigorous efforts to contain antibiotic resistant pathogens must be implemented. Hand hygiene is obviously the cornerstone of such efforts and use of personal protective equipment is also an evidence-based strategy aimed at preventing transmission.[82] The use of eradication strategies is only applicable for MRSA and may need to involve multiple body sites to prevent re-colonization.[27] Eradication of MRSA colonization should be considered for individual infants as the rate of progression to active disease can range from 18% to 80%.[86] If staff is linked to an outbreak and ongoing transmission of MRSA is demonstrated despite implementation of other infection control strategies, eradication of staff colonization may be indicated.[27] Finally, minimizing exposure to potentially modifiable risk factors such as central venous catheters should be implemented as described in Table 4.

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Synposis

Antimicrobial resistant pathogens are of increasing concern in the NICU population. A myriad of resistance mechanisms exist in microorganisms and management can be complex as broad spectrum antibiotics are increasingly needed. Control and prevention of AROs require an interdisciplinary team with continual surveillance. Judicious use of antibiotics, minimizing exposure to risk factors, when feasible, and effective hand hygiene are crucial interventions to reduce infection and transmission of AROs.

Table 1

Commonly Used Antibiotics in the NICU and Mechanisms of Action and Resistance

Major Classes of Antibacterial Agents	Examples of Specific Antimicrobial Agents	Mechanisms of Action	Mechanisms of Resistance
β-lactam agents • Penicillins • Cephalosporins • Carbapenems	• Penicillin/ Ampicillin/ Oxacillin • 1st generation: Cefazolin • 2nd generation: cefoxitin • 3rd generation: cefotaxime • Meropenem/ Imipenem	Interfere with bacterial cell wall synthesis by binding to transpeptidase active site of PBP	• Acquisition of β-lactamases which hydrolyze β-lactam ring • Mutations in PBP • Loss of Porins
Aminoglycosides	• Gentamicin • Tobramycin • Amikacin	Interfere with protein synthesis by binding to 30S ribosomal subunit	Acquisition of aminoglycoside modifying enzymes which alter drug side chains
Glycopeptides	Vancomycin	Interfer with bacterial cell wall synthesis by binding to C terminal D-alanine-D-alanine	Mutation in terminal component of cell wall leading to alteration from D-alanine-D-alanine to D-alanine-D-lactate

Note: PBP penicillin binding proteins

Table 2

Comparison of Community- associated vs. Hospital-associated MRSA

Characteristic	Community-associated	Hospital-associated	Comment
mecA	present	present	Encodes for PBP2a
SCC*mecA*	IV and V Relatively small ~ 20 kb	I, II, III Relatively large > 30 kb Carry additional resistance genes	USA300 most common CA clone
Resistance pattern	Resistant to: Oxacillin and other β-lactam agents	Resistant to: Oxacillin and other β-lactam agents Resistant to: Rifampin Gentamicn Erythromycin Tetracycline Clindamycyin Trimethorpim sulfamethoxazole	CA strains increasingly resistant

Note: SCC staphylococcal chromosomal cassette, CA community-acquired

Table 3

CDC Principles for Judicious Antibiotic Use: Relevant NICU Examples

'Get Smart' Principles	**Examples for the NICU**
Timely antibiotic management • Accurately identify patients who need antibiotic therapy • Obtain appropriate cultures prior to start of antibiotics • Administer antibiotics promptly	• Use biomarkers such as CRP to guide initiation of therapy. • Obtain simultaneous CVC and peripheral blood cultures when possible. • Obtain sufficient blood culture volumes, i.e., > 0.5 mL.
Appropriate selection, administration, and de-escalation of therapy • Make empiric choices based on local antibiograms • Do not give therapy with overlapping activity • Give the Right Dose and Interval • Stop therapy promptly if indicated by culture results • Review and adjust antibiotics at all transitions of care • Monitor for toxicity and adjust therapy accordingly	• Change vancomycin to oxacillin once infection with MSSA determined. • Aim for higher vancomycin troughs (15–20 mcg/mL) for suspected meningitis. • Discontinue post-operative prophylaxis after 48 hours. • Avoid redundant anaerobic spectrum coverage (e.g., metronidazole and piperacillin/tazobactram).
Access to expertise at point of care • Develop and make available expertise in antibiotic use • Ensure expertise is available to all physicians at the point of car	• Develop an antimicrobial stewardship team incorporating neonatology, clinical pharmacy, hospital epidemiology infectious diseases, and nursing services. • Obtain infectious diseases consultations.
Improved data monitoring and transparency • Monitor and feedback data regarding antibiotic utilization and adverse events • Make data visible to interdisciplinary care team.	• Provide NICU-specific antibiograms for common pathogens. • Measure and feedback data on antibiotic prescribing to neonatologists.

Table 4

Infection Control Strategies Aimed at Reducing Acquisition and Transmission of Antimicrobial Resistant (AMR) Pathogens

Major Infection Control Components	**Specific Strategies for Controlling Antimicrobial Resistant Organisms**	**Implementation of Specific Strategies**
Education	Ongoing education of interdisciplinary stake holders	Education of front line staff, including new hires
Identification of antibiotic resistant pathogens	Accurate microbiology laboratory strategies Rapid notification Judicious use of screening cultures and surveillance cultures for infants or NICU staff Monitoring Ill Staff and Visitors	Appropriate clinical cultures (when indicated) and access to molecular typing Consider screening cultures for high risk infants, e.g., transferred from other NICUs or hospitalized in close proximity to another infant infected or colonized with antibiotic resistant organism Consider surveillance cultures for staff if outbreak not halted by conventional measures Written policies for staff and visitors (including mothers) suspected or documented with AROs
Surveillance for AMR pathogens	Daily monitoring for epidemiologically significant AROs, e.g., MRSA and gram negative bacilli resistant to 3rd generation cephalosporins	Develop electronic surveillance for microbiology laboratory data NICU-specific antibiogram Track and trend resistance patterns
Containment of antibiotic resistant pathogens	Hand hygiene by staff and families Prompt initiation of *Contact Precautions*, i.e., staff don gown and gloves Environmental cleaning	Readily available hand hygiene products Observations of hand hygiene, including missed opportunities and staff feedback Adequate supplies of gowns and gloves Observations of transmission precautions, including missed opportunities and staff feedback Written policies for environmental cleaning, equipment cleaning (e.g., isolettes and radiant warmers)
Eradication of potential reservoirs of AMR pathogens	Consider eradication of MRSA colonization via topical antibiotics (e.g., mupirocin), topical disinfectants (e.g., chlorhexidine bathing)	Targeted eradication strategies may be indicated for endemic or epidemic colonization. Monitor for mupirocin resistance
Prevention of progression from colonization to infection	Reducing risk of infections via central line bundles	Implementation of evidence-based practices for insertion and maintenance of central lines including peripherally inserted central catheters Daily assessment for need for catheter and prompt removal of catheter when no longer required