Multidrug-Resistant *Pseudomonas aeruginosa* Infections

by

Abigail L. Tittle

A Master's Report Submitted to the Faculty of the

COLLEGE OF NURSING

In Partial Fulfillment of the Requirements
For the Degree of

MASTERS OF SCIENCE OF NURSING

In the Graduate College

THE UNIVERSITY OF ARIZONA

2010
STATEMENT BY AUTHOR

This master's project/report has been submitted in partial fulfillment of requirements for an advanced degree at The University of Arizona and is deposited in the University Library to be made available to borrowers under rules of the Library.

Brief quotations from this master's project/report are allowable without special permission, provided that accurate acknowledgment of source is made. Requests for permission for extended quotation from or reproduction of this manuscript in whole or in part may be granted by the head of the major department or the Dean of the Graduate College when in his or her judgment the proposed use of the material is in the interests of scholarship. In all other instances, however, permission must be obtained from the author.

SIGNED: Abigail L. Tittle

APPROVAL BY MASTER'S PROJECT DIRECTOR

This Master's Project has been approved on the date shown below:

Shu-Fen Wung, PhD, MS, RN, ACNP, BC, FAHA, FAAN  
Associate Professor  
Date:
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABSTRACT</td>
<td>5</td>
</tr>
<tr>
<td>CHAPTER ONE</td>
<td>7</td>
</tr>
<tr>
<td>Introduction</td>
<td>7</td>
</tr>
<tr>
<td>CHAPTER TWO</td>
<td>9</td>
</tr>
<tr>
<td>Literature Search</td>
<td>9</td>
</tr>
<tr>
<td>Literature Search</td>
<td>9</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>9</td>
</tr>
<tr>
<td>Mechanisms of Virulence</td>
<td>9</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa Infection</td>
<td>10</td>
</tr>
<tr>
<td>Cellular Resistance Patterns</td>
<td>12</td>
</tr>
<tr>
<td>Multi-Drug Resistance Patterns</td>
<td>13</td>
</tr>
<tr>
<td>CHAPTER THREE</td>
<td>15</td>
</tr>
<tr>
<td>Risk Factors for Multidrug-Resistant Pseudomonas aeruginosa Infection</td>
<td>15</td>
</tr>
<tr>
<td>Patient Risk Factors</td>
<td>15</td>
</tr>
<tr>
<td>Antibiotic Risk Factors</td>
<td>16</td>
</tr>
<tr>
<td>MDRPA and Poor Outcomes</td>
<td>16</td>
</tr>
<tr>
<td>CHAPTER FOUR</td>
<td>19</td>
</tr>
<tr>
<td>Infection Control</td>
<td>19</td>
</tr>
<tr>
<td>Important Concepts in Infection Transmission</td>
<td>19</td>
</tr>
<tr>
<td>Infection Control Practices</td>
<td>19</td>
</tr>
<tr>
<td>Treatment Strategies</td>
<td>21</td>
</tr>
</tbody>
</table>
Table of Contents (Continued)

Treatment with Appropriate Initial Combination Antibiotics ........................................ 21

Colistin (Polymyxin E) and Polymyxin B ................................................................. 24

Colistin ..................................................................................................................... 24

Aerosolized Inhaled Colistin Antibiotic ................................................................. 25

Polymyxin B ............................................................................................................. 25

Side Effects ............................................................................................................. 26

CHAPTER FIVE ......................................................................................................... 28

The Advanced Practice Nurse and Infection Control .............................................. 28

Conclusion .............................................................................................................. 29

APPENDIX A ........................................................................................................... 30

RECOMMENDATIONS FOR MANAGEMENT OF MULTIDRUG-RESISTANT

Pseudomonas aeruginosa ....................................................................................... 32

APPENDIX B ........................................................................................................... 33

TREATMENT RESEARCH TABLE ....................................................................... 34

EPIDEMIOLOGICAL RESEARCH TABLE ........................................................... 35

REFERENCES ......................................................................................................... 38
Abstract

*Pseudomonas aeruginosa* is an important cause of hospital acquired infections and the second most common pathogen isolated in intensive care unit infections. Surveillance of *Pseudomonas aeruginosa* has exposed rising trends in multidrug-resistance. Multidrug-resistant forms of *Pseudomonas aeruginosa* are associated with higher mortality and morbidity compared to other bacterial pathogens. Resistant *Pseudomonas aeruginosa* is a public health problem that affects many countries of the world. The purpose of this paper is to review the epidemiology, infection control practices, and treatment strategies for multidrug-resistant *Pseudomonas aeruginosa* (MDRPA) infections.

A search was conducted using MEDLINE (PubMed). Keywords included MDRPA, treatment, epidemiology, and infection control. MDRPA yielded 685 results. The search was narrowed with the inclusion criteria of a time parameter of 2005 – current, age greater than 18, human studies, English language, epidemiology, infection control and treatment of multidrug-resistant *Pseudomonas aeruginosa*, or multidrug-resistant gram-negative bacteria. Exclusion criteria included cystic fibrosis population, extended care facilities. Reference lists were reviewed for important articles to be included.

MDRPA is becoming more common, with an average increase in resistance patterns of 10% from 1992 to 2004. Infection control practices have a profound impact on the spread of these opportunistic infections. Treatment strategies in the form of new antibiotics are limited; and therefore, current management becomes increasingly important. Effective treatment includes prevention, source control, starting combination antibiotics that have adequate
coverage, using successful synergistic antibiotic combinations, including Polymyxin B and E antibiotics.
Chapter One
Introduction

*Pseudomonas aeruginosa* is rarely colonized in healthy humans, but it is an important cause of hospital acquired infections, especially in immunocompromised patients, burn patients or cystic fibrosis patients (Blondel-Hill, Henry & Speert, 2007). *Pseudomonas aeruginosa* is the second most common pathogen isolated as healthcare-associated infections such as healthcare-associated pneumonia and ventilator-associated pneumonia (NNIS, 2004).

Multidrug-resistant *Pseudomonas aeruginosa* (MDRPA) is a public health problem that affects many countries of the world. MDRPA is becoming more common, with an average increase in resistance patterns of 10% from 1986 to 2004 in the United States (NNIS, 2004). The European Antimicrobial Resistance Surveillance System (EARSS) reports an overall MDRPA rate of 7.4% to five commonly used anti-pseudomonas antibiotics, such as β-lactams, ciprofloxacin, levofloxacin, imipenem, and amikacin, with single antibiotic resistance patterns as high as over 50% in Romania, Bulgaria, and Poland. Ten of 23 countries in Europe reported over 25% MDRPA to fluoroquinolones (Rossolini & Mantengoli, 2008). MDRPA rates in Latin America are from 21% to 60%, with *Pseudomonas aeruginosa* being the third most common isolate from hospitalized patients (Sader, Jones, Gales, Silva, & Pignatari, 2004). The National Epidemiological Surveillance of Infectious Disease (NESID) of Japan has found *Pseudomonas aeruginosa* resistant rates of 11-13% (Izumida et al, 2007). The National Nosocomial Infection Surveillance System (NNIS) of the United States reports *Pseudomonas aeruginosa* antibiotic resistant rates in the ICU to be 14% to 35% (NNIS, 2004).
Treatment options for MDRPA infections are limited and therefore, they become more difficult and costly to treat (McGowan, 2006). MDRPA infections can adversely affect patient outcomes. Additionally, MDRPA infections are being considered hospital-acquired conditions that may not be covered for reimbursement (McNutt et al., 2010). Infection control practices have a profound impact on the spread of these opportunistic infections. Treatment strategies in the form of new antibiotics are limited; therefore, the manner in which current antibiotics are used becomes increasingly important. Healthcare providers and institutions must take appropriate action to protect patients at risk for MDRPA infections.

Definition of Terms. *Pseudomonas aeruginosa* is a gram-negative bacterium. It is common in binominal nomenclature to shorten the first Latin name or the *genus* and spell out the second name which is the species, such as *P. aeruginosa*. A Pan-resistant form of *P. aeruginosa* is considered resistance to all four classes of antibiotics: β-lactams, carbapenems, aminoglycosides and fluoroquinolones, commonly used to treat *P. aeruginosa* infections.

MDRPA is defined by the CDC as resistance to one or more classes of antimicrobial agents (Siegel et al., 2006). In the literature, the term multidrug-resistant gram-negative (MDRGN) or multidrug-resistant organism (MDRO) are often used to include MDRPA. MDRGN include multidrug-resistant gram-negative bacteria such as, *P. aeruginosa*, *Acinetobacter baumannii*, *Stenotrophomonas maltophilia*, and *Burkholderia cepacia* (McGowan, 2006). MDRO is defined as a broad category of bacteria resistant to common antibiotics (Siegel et al., 2006).
Chapter Two

Review of the Literature

Literature Search

A search was conducted using MEDLINE (PubMed). Keywords included multidrug resistant *P. aeruginosa*, treatment, epidemiology and infection control. Multidrug-resistant *P. aeruginosa* yielded 685 results. The search was narrowed with the inclusion of a time parameter of 2005- current. This search was further limited to age greater than 18. Further limitations included human studies, English language, and non-cystic fibrosis population. No limitations were placed on location, co-morbidities, sex or race. References were reviewed for relevant articles. A total of fifty two articles were selected for review.

*Pseudomonas aeruginosa*

*P. aeruginosa* is hydrophilic and can be found in moist environments, such as sinks, vegetables, fruit juice, and river water. However, these reservoirs do not lead to gastrointestinal colonization unless the host is immunocompromised or has been on a prolonged course of antibiotics. *P. aeruginosa* has intrinsic resistance to many antibiotic classes and has the that may evolve during antibiotic therapy (Blondel-Hill, Henry & Speert, 2007).

Mechanisms of Virulence

Because *P. aeruginosa* is not a part of the normal human flora, it possesses innate mechanisms of infection and virulence. *P. aeruginosa* uses flagellum, and multiple cell surface pili, to gain entry and attach to host cells surfaces (Driscoll, Brody, & Kollef, 2007). Additionally, alginate secretion, an overproduction of extracellular polysaccharides that protect the bacteria, impedes the host’s ability to clear the bacteria through phagocytosis and inhibits
neutrophils (Driscoll et al., 2007). Furthermore, alginate secretion production aids in the formation of biofilm. Biofilm is a cluster of microcolonies of bacterial cells that are encased in a polymer matrix which attaches to a surface. The biofilm has been found on indwelling medical devices and patient airways. The biofilm, mechanism of virulence has been implicated in the following infections; respiratory infections, urinary tract infections (UTIs), vascular access devices, kidney stones, and endocarditis (Driscoll et al., Blondel-Hill, Henry, & Speert, 2007). Another function that *P. aeruginosa* acquires is bacterial communication. Quorum sensing is communication of bacteria via an intracellular signal which allows for the collective regulation of important functions, such as biofilm formation, gene transcription, and protein synthesis, which increases virulence (Driscoll et al.).

Virulence is further augmented by the Type III secretion system. This system works by injecting effector proteins into the epithelial and host cells that alters immune response, and promotes cell injury and cell death (Driscoll, Brody, and Kollef, 2007). Exoenzymes and exotoxins increase *P. aeruginosa* virulence by increasing host cell death, promoting ciliary dysfunction in the respiratory tract, acting as pro-inflammatory agents and creating oxidative damage (Driscoll et al., 2007). *P. aeruginosa* infections with these virulence factors are associated with acute invasive infections, which have increased mortality, relapse of infection, sepsis and more severe lung injury (Ruxana et al., 2005).

**Pseudomonas aeruginosa Infection**

*P. aeruginosa* is an opportunistic infection; it is not colonized as normal flora in healthy humans. It can live on contaminated items, such as respiratory equipment, electronic thermometers, computers, beds and healthcare worker’s hands (Dwivedi et al., 2009). It can be
transmitted through contaminated medicated solutions and blood products (Blondel-Hill, Henry, & Speert, 2007). *P. aeruginosa* uses invasive devices as a portal of entry, such as urinary catheters, endotracheal tubes, and vascular access devices (Yetkin, Otlu, Cicek, Kuzucu, & Durmaz, 2006).

Neutropenic patients and patients who have received frequent antibiotics have been found to have gastrointestinal colonization of *P. aeruginosa*, and it is thought this may be the cause of bloodstream infections and patient-to-patient transmission in as many as 31% of ICU patients (Johnsen et al., 2009).

*P. aeruginosa* is a serious infection that is found frequently in critically ill and immunocompromised patients. *P. aeruginosa* is the second most common bacterium isolated in the ICU (12.2%) (Sadler et al., 2004, Streit, Jones, Sader, and Fritsche, 2004). The most common *P. aeruginosa* infections are UTI (16%-35%), respiratory tract infections (18-34%), bacteremia (3.4%-13%), surgical site infections and wounds (9.5-25%) (Neuhauser et al., 2003, Gaynes et al., 2005, Yetkin, Otlu, Cicek, Kuzucu, & Durmaz, 2005). *P. aeruginosa* can cause meningitis following trauma or surgery, malignant otitis externa in diabetics, endocarditis or osteomyelitis in intravenous drug users, pneumonia in people with chronic obstructive pulmonary disease, and peritonitis (Blondel-Hill, Henry, and Speert, 2007). Also, systemic infections caused by *P. aeruginosa* in patients with major burn injuries are common and are associated with higher mortality than non *P. aeruginosa* infections (McPhee & Papadakis, 2009). As many as 60% of people with cystic fibrosis have chronic infections from *P. aeruginosa*, and it is considered the most prevalent infection in patients with cystic fibrosis (Blondel-Hill et al., 2007).
Cellular Resistance Patterns

Resistance patterns for *P. aeruginosa* are especially ominous due to its ability to rapidly develop resistance to multiple classes of antibiotics during treatment (Lister, Wolter, Hanson, 2009). Mechanisms of resistance focus on alteration in the *P. aeruginosa* outer bilayer and antibacterial enzymes. Bacterial mutations that promote antibacterial resistance evolve from natural selection of mutations that survive therapy or transfer of genetic material between bacteria through horizontal transfer. Genetic material can be transferred through three mechanisms: first, transformation; which is genetic material uptake and integration from the external environment, second, transduction which is when a viral vector transfers the genetic material; third, by conjugation, directly from cell to cell by a plasmid (Lister et al., 2009).

Protein channels called “porins” make the outer membrane of *P. aeruginosa* semi-permeable. Permeability is required to import nutrition into the bacterial cell, but it also allows antibiotics into the cell and leads to bacterial eradication (Lister et al., 2009). Therefore, *P. aeruginosa* down-regulates the expression of porins that are permeable to antibiotics. Impermeability mutations are implicated in resistance to carbapenem, aminoglycosides, colistin and quinolones (Lister et al.). Antibiotic resistance is also accomplished by reducing the accumulation of antibiotics inside the cell through active membrane efflux pumps (Lister et al.). Up-regulation and mutations of efflux pumps are influenced by sub-inhibitory levels of antibiotics and recent antibiotic therapy, resulting in increased minimum inhibitory concentrations (MICs) for antibiotic effectiveness (Blondel-Hill, Henry, and Speert, 2007). Efflux pump up-regulation and mutations have been associated with resistance to fluoroquinolones, β-lactams, and aminoglycosides (Lister et al.).
*P. aeruginosa* also expresses several chromosomal enzymes that degrade antibiotics. β-Lactamase is the enzyme capable of degrading β-Lactams (Lister et al., 2009). Metallo-β-lactamases and metallo-carbapenemases are responsible for carbapenem-resistant *P. aeruginosa* (Blondel-Hill, Henry, and Speert, 2007). Drug inactivation by enzyme is the most common mechanism for aminoglycoside resistance. Genetic materials for aminoglycoside-modifying enzymes are encoded on plasmids and are readily transferred between strains of *P. aeruginosa*. These enzymes contribute to resistance within multiple classes of antibiotics (Blondel-Hill et al., 2007). Enzymes that degrade antibiotics, upregulation of efflux pumps and down-regulation of porin channels make *P. aeruginosa* a serious challenge (Lister et al.).

**Multi-Drug Resistance Patterns**

Nosocomial infections due to *P. aeruginosa* are common in the critically-ill patient and multidrug-resistance patterns for these infections are on the rise. As discussed previously, *P. aeruginosa* has multiple patterns of resistance and all anti-pseudomonas antibiotic classes are affected. Two studies that evaluated surveillance data in over 50,000 *P. aeruginosa* isolates and found that multidrug-resistance rates have increased from 4% in 1993 to over 20% in 2002 (Obritsch, Fish, MacLaren & Jung, 2004, and Livermore, 2002). In a 36-month study, Vonberg and associates (2008) examined 503 cases of MDRGN infections during hospitalizations from 2002 to 2004 and found that *P. aeruginosa* accounted for 40.2% of MDRGN infections. It is disturbing that Vonberg and associates (2008) found 21% of the gram-negative bacteria were pan-resistant and transmission rates from patient to patient were 5%. Neuhauser and associates (2003) studied 35,790 gram-negative isolates recovered from ICU patients and found an overall increase in antibiotic resistance rate of 10% from 1994 to 2000, with fluoroquinolone resistance
increased from 23% to 29.5% and ciprofloxacin resistant rates increasing from 14% to 24%.

Gaynes (2005) reviewed over 400,000 bacterial isolates associated with nosocomial infections from ICUs in the United States and found resistant patterns of *P. aeruginosa* significantly increased from 13% to 23% from 1986 to 2003. Similarly, Data from the NNIS (2004) system in the United States from 1986 to 2003 showed an increase in resistance for the commonly used anti-pseudomonas antibiotics; quinolones, imipenum, ceftazidime, and levoflaxacin were 9%, 15%, 20%, and 35%, respectively. Comparatively, an antimicrobial surveillance program gathered bacterial strains from 25 ICUs in North America, and reported similar drug resistant rates of 3.1% for amikacin, 24.8% for ciprofloxacin, 16% for imipenem, and 19.3% for ceftazidime (Streit, Jones, Sader, Fritsche, 2004).

Similar patterns are being found in all parts of the world. For example, Europe, Japan, North America and Latin America have reported a 10% or more increase in antibiotic resistance over the last decade, with some areas reaching a critical 50% resistance to common antibacterial therapy (Sader, Jones, Gales, Silva, Pignatari, 2004). Although resistance rates vary from report to report, the unifying message is that resistance rates are increasing at an alarming pace.
Chapter Three

Risk Factors for Multidrug-Resistant *Pseudomonas aeruginosa* Infection

**Patient Risk Factors**

The risk factors for MDRPA are closely related to the invasive nature of the ICU and the critical patients who require this level of care. Patient’s risk factors for opportunistic MDRPA infections include broad risk factors, such as immunosuppression with greatest risk for patients undergoing chemotherapy or bone marrow ablation, patients with cystic fibrosis, hemodialysis, burns, sepsis, UTI, malignancy, prolonged exposure to broad spectrum antibiotics within the last three months, hospitalization in the preceding year, and advanced age (Noué´r, Nucci, de-Oliveira, Pellegrino, Moreira, 2005; Blondel-Hill, Henry, & Speert, 2007; Yetkin, Otlu, Cicek, Kuzucu, and Durmaz, 2006).

For example, Pop-Vicas, Strom, Stanley and D’Agata (2008) studied 172 cultures from 67 chronic hemodialysis patients, and found an abnormally elevated, 16% incidence of bowel colonization with MDRPA. Therefore, this reveals a high incidence of colonization in patients with a chronic immune suppression state that puts patients at risk for active infections with MDRPA. Further, Yetkin, Otlu, Cicek, Kuzucu, and Durmaz (2006) studied 105 Pseudomonas strains in 80 patients over a one-year period in an University hospital in Turkey and found that 48% of patients with MDRPA infections had an underlying disease: 32% had a chronic illness; 20% had a malignancy; and 71% had an invasive device, representing some form of a weakened immune system. Ohmagari and associates (2005) studied cancer patients and found significant risk factors for MDRPA including: a history of previous *P. aeruginosa* infection, steroid use in the last 30 days, chronic obstructive pulmonary disease and leukemia. In comparison, Lodise
and associates (2007) identified prolonged hospital stay, prior culture positive for *P. aeruginosa*, and prior antibiotic exposure as significant risk factors for MDRPA respiratory infection.

**Antibiotic Risk Factors**

There is a close link between antibiotic therapy and the development of multidrug-resistant strains of *P. aeruginosa*. As discussed previously, *P. aeruginosa* reacts to antibiotics with various resistance mechanisms. Noue’r and associates (2005) found patients treated with fluoroquinolone antibiotics had a statistically higher rate of MDRPA that produced extended spectrum β-lactamase. Ohmagari and associates (2005) found a correlation between the length of carbapenem therapy of over seven days and the development of MDRPA. Similarly, Chien and associates (2009) monitored isolates from patients requiring prolonged mechanical ventilation and exposure to antibiotics, and found therapy with ceftazidime was related to resistant strains of *P. aeruginosa*. Therefore, exposure to anti-pseudomonal antibiotics is a risk for resistance and the risk has been related to the length of exposure with the highest risk associated with carbapenems and fluoroquinolones.

In summary, some common themes emerge as risk factors for MDRPA infections. Patient risk factors surround a weakened or breached immune system, a chronic illness or prolonged exposure to antibiotics. Specific risk factors for MDRPA infection include prolonged hospital length stay, prior cultures with *P. aeruginosa* and prior exposure to anti-Pseudomonas antibiotics, specifically, fluoroquinolones and carbapenems.

**MDRPA and Poor Outcomes**

As *P. aeruginosa* becomes increasingly resistant, the cost to our healthcare system increases. Understanding the burden of multidrug-resistance infections play an important role in
prompting hospitals and providers to follow treatment guidelines, track data, maintain policies to prevent transmission and stimulate interest in new treatment options (Cosgrove, 2006). Shorr (2009) performed a meta-analysis of 21 original studies and found MDRGN infections increased ICU mortality, increased length of stay and costs. Similarly, Aloush, Naron-Venzia, Seigman-Igra, Cabili, and Carmeli (2004) studied 82 patients with MDRPA over a 10 month period and found in addition to increased mortality, they also had an increase in procedures, and on discharge had poorer function and increased rate of discharge to a rehabilitation center as compared to patients with similar infections that were susceptible to antibiotics. Likewise, Ohmagari and coworkers (2005) found cancer patients with COPD infected with MDRPA required significantly more ventilation days as compared to non MDRPA infected patients (21 days vs. 1.5 days, respectively). Shorr (2009) evaluated eight studies specific to MDRPA infections compared to susceptible \textit{P. aeruginosa} infections and found a four-to five-fold increase in mortality and a significantly longer length of stay with an average of six additional days in patients with MDRPA infections.

Cost may take several variables into account, for example, antibiotic cost, procedural costs, radiological, total hospital cost, nursing hours, and rehabilitation costs (Shorr, 2009). Further, cost may be misleading as early mortality may decrease cost (Shorr, 2009). Gasink and associates (2006) researched fluoroquinolone resistant \textit{P. aeruginosa} infections from 1999 to 2000 and found that the total hospital charges average of 62,325 dollars for resistant infections versus 48,734 dollars for susceptible infection patients. Similarly, Lautenbach and coworkers (2006) evaluated the burden of imipenem resistant strains of \textit{P. aeruginosa} compared to susceptible strains of \textit{P. aeruginosa} and found a statistically significant difference in median
hospital costs. The median hospital cost was 81,330 dollars for imipenum resistant *P. aeruginosa* infections and 48,381 dollars for imipenum susceptible *P. aeruginosa* infections. Similarly, Mauldin and associates (2010) studied 662 hospital acquired infections from 2000-2008 and found a significant median increase in cost of $38,121 per patient with resistant gram-negative hospital acquired infections. Mauldin and associates (2010) also found significant differences in cost to treat patients with surgical site infection or pneumonia with MDRPA compared to the cost of treating similar susceptible *P. aeruginosa* infections.

In summary, multidrug-resistant *P. aeruginosa* places a heavy burden on our healthcare system and the patients who are affected. These above studies illustrate that there is increased mortality, length of hospital stay, and cost associated with MDRPA infections. Other difficulties encountered with MDRPA infections include increased need for rehabilitation on hospital discharge and increased renal complications from antibiotic toxicities (Shorr, 2009).
Chapter Four

Infection Control

*Important Concepts in Infection Transmission*

Transmission of infection in the healthcare setting requires three components; a reservoir, a susceptible host with a portal of entry, and a mode of transmission. Because of this relationship within the healthcare environment, precautions must be taken to protect patients from transmission of infection. Further factors that affect multidrug-resistant organisms transmission and persistence of resistant strains are determined by the vulnerability of patients, selective pressure exerted by antimicrobial use, increased potential for transmission from larger numbers of colonized or infected patients (“colonization pressure”) and the impact of implementation and adherence to prevention efforts (Siegel, Rhinehart, Jackson, Chiarello, & The Healthcare Infection Control Practices Advisory Committee, 2006). Transmission is most common through the hands of healthcare workers, but can also occur from patient-care devices, or equipment that is not thoroughly cleaned between uses (Seigel et al., 2007).

*Infection Control Practices*

Harris, McGregor, and Furuno (2006) report the incidence of transmission of MDRPA infection is from 18% to 64%. Similarly, Dwiredi and associates (2009) researched transmission rates and revealed that 79% of the *P. aeruginosa* isolates cultured from healthcare workers matched isolates from patients. Johnson and coworkers (2009) found patient to patient via healthcare workers transmission rate was 31%. The CDC recommends the use of contact isolation precautions before entering a patient’s room and strict hand hygiene for all multidrug-
resistant organisms. Similarly, Vonberg and associates (2008) recommends barrier isolation until cultures are negative for MDRPA.

The CDC’s 2006 guidelines for the management of multdrug-resistant infection control include the use of a comprehensive infection control program that includes administrative involvement, judicious use of antibiotics, laboratory support, surveillance, education, performance measures, and environmental measures. Bukholm, Tannaes, Kjelsberg and Smith-Ericksen (2002) used multiple approaches, requiring the coordination of administration, nursing, providers and environmental control to eradicate an outbreak of MDRPA in a 10-bed ICU.

The surviving sepsis campaign guidelines along with the Infectious Disease Societies of America (IDSA) recommend aggressive culturing including taking blood, sputum, cerebrospinal, wound or other body fluid source cultures before starting antibiotics and with new signs of clinical infection (Adachi et al., 2009, Vonberg et al., 2008, Dillinger et al, 2004, and Mandell et al., 2007). Once the source is identified, the infection should be managed to include draining the abscess, discontinuing the invasive lines, or wound debridement (Dellinger et al., 2004). There is also strong support from the CDC and IDSA for the use of bundled evidence-based clinical practices for ventilator-associated pneumonia and central venous line associated bloodstream infections (Siegel, Rhinehart, Jackson, Chiarello, & The Healthcare Infection Control Practices Advisory Committee, 2006). Interventions in the ventilator-associated pneumonia bundle include: appropriate antibiotics that are narrowed with cultures and sensitivities, avoid or discontinue endotracheal intubation, if possible; maintain head-of-bed at 45-degree angle; utilize post pyloric feeding, oral antiseptics, stress ulcer and deep venous thrombosis prophylaxis and daily sedation lightening.
The CDC (2002) recommends a bundle of central venous access device infection control measures. The CDC recommends using the subclavian or internal jugular site. The insertion site should show no evidence of phlebitis. It is recommended to use antibiotic impregnated central line catheters, hand hygiene before the procedure with aseptic technique during the procedure. The CDC recommends skin antisepsis with 2% chlorhexadine at the insertions site and a chlorhexadine impregnated sponge for catheter dressings. Sutureless securing devices are recommended to keep the catheter in place. The CDC bundle includes changing out the central line every seven days or with signs of infection.

The prevention of MDRPA is a national concern and each institution has a responsibility to protect patients at risk. The infection control requires dedication and multidisciplinary team work with individualized interventions. Guidelines on ventilator-associated pneumonia, sepsis and central line infection control provide a starting point for infection control programs.

Treatment Strategies

Important concepts in antibiotic treatment of MDRPA include treating initially with appropriate combination antibiotics, the use of synergy with antibiotic agents and the use of the alternative antibiotic class of polymyxins. De-escalating of antibiotics may be considered after susceptibility reports are available.

_Treatment with Appropriate Initial Combination Antibiotics_

Initial treatment of infections with appropriate antibiotics has been shown to improve mortality (Micek et al., 2005, Kollef, Sherman, Ward, and Fraser, 1999). Kollef and associates (1999) studied 655 patients and found that infection-related mortality in patients treated with inappropriate compared with appropriate antibiotics was 42% and 17.7%, respectively.
Likewise, Micek and coworkers (2005) evaluated 305 patients over a six-year period and found mortality was significantly higher for the inappropriate versus appropriate antibiotic group, 30.7% vs. 17.8%, respectively.

The Infectious Disease Society of America also recommends initially treating infections with appropriate antibiotics. When initiating treatment for \textit{P. aeruginosa}, it is recommended to use two antibiotics that the patient has not taken within the last thirty days, from two different classes, using local biograms, and then narrowing according to sensitivity results (American Thoracic Society and Infectious Diseases Society of America, 2005). Broad spectrum antibiotics that cover likely pathogens should be started and antibiotic therapy should be re-evaluated at 48 and 72 hours and narrowed if possible (Dellinger et al., 2004).

Continued combination therapy throughout treatment is controversial. Chamot, Amari, Rohner, Delden (2003) researched monotherapy verses combination therapy and found a significant improvement in mortality at 30 days for combination therapy. In contrast, Safdar, Handelsman, and Maki (2004) completed a meta-analysis on 17 studies and found no statistical significant difference between monotherapy compared with combination therapy. It is not recommended that aminoglycosides, such as gentamicin, tobramycin and amikacin, be used alone but rather used in combination with other common classes of antibiotics to treat \textit{P. aeruginosa} infection (Driscoll, Brody, Kollet, 2007). Combinations of antibiotics that are recommended consist of an antipseudomonal β-lactam, carbapenem, or third generation cephalosporin with an aminoglycoside or fluoroquinolone rather than aminoglycoside and fluoroquinolone combinations, to provide adequate therapy and improve patient outcomes (Obritsch, Fish, Maclare, and Jung, 2005, Dellinger et al., 2004, Maeda et al, 2008).
Antibacterial therapy should be administered in a timely manner within one hour for patients with sepsis, and four hours for patients with pneumonia (Dellinger et al.).

As resistance rates continue to climb and few new antibiotics are on the horizon, choices of treatment are limited. Synergy with anti-pseudomonal antibiotics drugs have been observed when combined in vitro against MDRPA with successful clinical application (Maeda et al. 2008). Maeda and associates (2008) evaluated the use of three-drug combinations and found bacteriostatic effects. The first combination of antibiotics found to be effective is; ceftazidime, aztreonam and amikacin. The second combination of bacteriostatic antibiotics includes piperacillin, piperacillin-tazobactam and aztreonam. These combinations led to improved clinical resolution of infections (Maeda et al.). Obritsch , Fish, Maclare, and Jung (2005) reviewed 14 studies for synergistic antibiotic combinations for treatment of MDRPA. Two-and three-drug combinations were included with variable synergy rates of 0% with β-lactam plus fluoroquinolone, 43-80% with three β-lactams, and 43-100% with two β-lactams plus amikacin. Trends in synergy studies point toward certain successful combinations, such as β-lactams combined with additional β-lactams, or β-lactams plus amikacin and ceftazidime. Colistin (polymyxin E) combined with adjunctive therapy, such as β-lactams, ciprofloxacin or rifampin, may be useful in MDRPA as well (Obritsch et al., 2005). Ostronoff and associates (2006) used polymyxin B combined with rifampin for durations of 19 and 21 days with bacteriological cure in two patients on chemotherapy with MDRPA. Colistin and tigecycline was used to treat MDRPA osteomyelitis after an allogeneic bone marrow transplant and resulted in resolution of the infection (Stanzani, 2007). With combinations of antibiotics, toxicity is unpredictable and should be monitored.
Colistin (Polymyxin E) and Polymyxin B

The increasing rate of antibiotic resistance has forced providers to re-evaluate the use of the older antibiotics, colistin (polymyxin E) and polymyxin B. Colistin and polymyxin B are lipopeptide antibiotics and interact with the lipopolysaccharide of the outer membrane of the gram-negative bacteria (Zavascki, Goldani, Li, Nation, 2007). Colistin binds to the cell membrane and has a disruptive effect causing permeability changes leading to cell death (Zavascki et al., 2007). The Polymyxins have been used as implanted pellets for osteomyelitis. The Polymyxins have been used as inhaled aerosolized treatments for patients with cystic fibrosis and have recently been studied for pneumonia with non-cystic fibrosis patients as well (Sabuda et al., 2008).

Colistin

Koomanachai and coworkers (2007) studied 93 patients with MDRGN isolates and 78 patients received colistin at an average dose of 5mg/kg/day intravenous divided into two daily doses. Results from this study showed an 80% clinical response and 95% microbiological response. Clinical response was defined as resolution of symptoms of infection and microbiological response was defined as cultures negative for MDRPA. Mortality was 46.2% in the colistin group vs. 80% in the non-colistin group (Koomanachai et al., 2007). Similarly, Maeda and associates (2008) examined 1,720 isolates of P. aeruginosa and found four strains that were resistant to eight widely used antibiotics. Colistin was the only antimicrobial agent that provided bacteriostatic effects (Maeda et al., 2008). Sabuda and colleagues (2008) retrospectively reviewed 22 patients with MDRPA who received IV colistin at an average dose
of 3.7 mg/kg/day and in 12 patients received additional nebulized colistin and found a clinical resolution of infection in 67% of patients.

**Aerosolized Inhaled Colistin Antibiotic**

Most *P. aeruginosa* infections are found in the respiratory tract (Streit, Jones, Sader, Fritsche, 2004). Therefore, using colistin as an aerosolized nebulizer antibiotic treatment has been researched and found to improve outcomes (Czosnowski et al., 2009, Sabuda et al., 2008, Kwa, Loh, Low, Kurup, Tam, 2005). In a study by Sabuda and associates (2008), 12 patients received colistin solely via nebulization to treat MDRPA infection, and 67% had clinical response with a resolution of infection. The inhaled dose of colistin was 150 mg every 12 hours, and it was suggested to use a bronchodilator prior to colistin nebulizer (Sabuda et al.). Similarly, Michalopoulos and colleagues (2005) studied eight patients received aerosolized colistin, dosed at 1.5 to 6 million IU three times per day and found a clinical resolution of infection in seven patients. Similarly, Czosnowski et al. (2009) treated 60 episodes of pneumonia MDRPA with aerosolized colistin as adjunctive therapy and had a 71% of clinical cure. Further, Czosnowski and associates (2009) successfully used nebulized colistin in patients who had failed intravenous therapy with success.

**Polymyxin B**

In clinical practice, colistin (polymyxin E) is more widely used than polymyxin B, therefore, research on polymyxin B is sparse (Zavascki, Goldani, Li, Roger & Nation, 2007). In a study by Furtado and associates (2007), polymyxin B was used in 74 patients with MDRPA and a clinical resolution of infection was found in 47.3% of patients. Polymyxin B dosage should be adjusted based on creatinine clearance (CrCl). Furtado and associates (2007) provide
dosage information used for patients with various degrees of kidney function. Furtada and colleges recommend the starting dose of polymyxin B at 1.5-2.5 mg/kg/day. If Crcl is 30-80 ml/min, the polymyxin B dose should be adjusted to 1.0-1.5 mg/kg/day. When Crcl is further reduced to <30 ml/min, the polymyxin B dose should be decreased to 1 mg/kg/day. In a review of five articles, Zavascki and colleagues (2007) reported that in MDRPA infected patients treated with polymyxin B, the mortality was 20% and bacterial clearance was 80%. These findings suggest that polymyxin B is effective for the treatment of MDRPA infection.

Side Effects

Once thought to be highly nephrotoxic and neurotoxic, new studies have found colistin and polymyxin B to be safe (Falagas & Kasiakou, 2006, Maeda et al., 2008, Sabuda et al., 2008). Nephrotoxicity is defined as an increase in serum creatinine of 50%, new hematuria, or new proteinuria (Falagas & Kasiakou). Neurotoxicity is defined as paresthesia, respiratory apnea, or neuromuscular blockade. Falagas and Kasiakou completed a literature review on toxicity of polymyxins from 1950 to 2005. Falagas and Kasiakou found that studies before 1995 used doses of polymyxin E and B significantly higher than updated dosing recommendations. Nephrotoxicity rate was 10-18% in studies performed after 1995. Furthermore, Falagas and Kasiakou found neurotoxicity rate was 27% from early studies, with no reports of neurotoxicity in the last 15 years. Sabuda et al. (2008) reported that 56% of patients receiving IV colistin at an average dose of 3.7 mg/kg/day had a doubling of creatinine, however, the creatinine levels after completion of colistin were not available. Koomanachai and coworkers (2007) reported a 30% nephrotoxicity in patients receiving colistin at an average dose of 5 mg/kg/day in two divided doses. These authors reported that 17 of the 24 patients with nephrotoxicity had
predisposing factors, such as other nephrotoxic drugs, chronic kidney disease, and hypovolemia. These authors also observed nephrotoxicity to be reversible after completion of colistin therapy. Similarly, Montero et al. (2009) examined 121 MDRPA patients treated with colistin and nephrotoxicity rate was determined to be 8.3%. The associated factors for nephrotoxicity were chronic renal insufficiency, diabetes, and aminoglycoside use. Potential adverse events related to nebulized colistin may include neurotoxicity, nephrotoxicity, bronchospasms, or respiratory distress. However, no adverse events associated with nebulized colistin have been reported (Michalopoulos et al. 2005).
Chapter Five

The Advanced Practice Nurse and Infection Control

The CDC’s guidelines on infection control also include the role of an infection-control liaison nurse. This advanced practice nurse (APN) will play a crucial role in infection control measures and antibiotic stewardship. Infection control requires a multidisciplinary approach, and the APN is well suited to arrange collaboration within a multidisciplinary team. The APN acts as an infection-control liaison who collects infection resistant rates, reviews current infection control measures and keeps hospital policy current, works with administrators to approve the needed staffing, surveillance and support required to carry out measures to protect patients from nosocomial infections. The APN can work with the environmental department in monitoring and reviewing adequate cleaning practices for *P. aeruginosa*. The respiratory department will also need to be involved in reviewing cleaning practices and routine monitoring for reservoirs on respiratory equipment. Further, the APN can work with the education team to educate all health care workers on the importance of hand hygiene, and compliance with infection control practices. Finally, the APN can work with the medical team and pharmacy to review the microbiological studies, order the correct isolation level and follow evidence based antibiotic prescribing practices, such as initiating appropriate antibiotics, deescalate antibiotics to culture sensitivities, avoid antibiotics with high resistance profiles, and keep length of antibiotic treatment to shortest effective course.
Conclusion

Increasing MDRPA nosocomial infections is a prominent public health concern around the world. *P. aeruginosa* infection is opportunistic and is one of the most common healthcare associated pathogens, particularly in the ICU.

Risk factors for MDRPA include recent hospitalization, prior cultures with *P. aeruginosa*, and exposure to anti-Pseudomonal antibiotics particularly fluoroquinolones and carbapenems. The most common source of transmission is through the hands of healthcare workers from patient-to-patient. To avoid the spread of MDRPA to other vulnerable patients, strict contact isolation practices are recommended.

With few new antibiotics on the horizon and the rising incidence of MDRPA worldwide, it becomes increasingly important to utilize strategies that will minimize the effects of resistance on the vulnerable patients and our overstressed healthcare system. Effective treatment includes prevention, source control, starting combination antibiotics that have adequate coverage, using successful synergistic antibiotic combinations, including Polymyxin B and E antibiotics.
APPENDIX A

Recommendations for Management of Multidrug-Resistant *Pseudomonas aeruginosa*
Recommendations for Management of Multidrug-Resistant *Pseudomonas aeruginosa*

- **Recognize patients at risk**
  - Immunocompromised
  - Burn injury
  - Cystic Fibrosis
  - End stage renal disease with hemodialysis
  - Advanced age
  - Hospitalized within the last year
  - Broad spectrum antibiotics within the last three months, fluoroquinolones, carbapenems
  - Invasive devices, central venous catheters, urinary catheter, endotracheal tube
  - History of *Pseudomonas aeruginosa* infection

- **Infection control**
  - Culture before starting antibiotics
  - Source control, drain abscess, discontinuing invasive lines, wound debridement
  - Contact isolation until negative cultures
  - Hand hygiene
  - Comprehensive infection control program with infection control-liaison nurse
  - Monitor environmental reservoirs such as respiratory equipment, sinks
  - Use infection bundles, ventilator acquired pneumonia and central venous access devices

- **Treatment Strategies**
  - Initial antibiotics; start with two antibiotics from different classes, not recently received
  - Recommended initial antibiotic combinations; antipseudomonal \( \beta \)-lactam, carbapenem, or 3\(^{rd}\) generation cephalosporin with an aminoglycoside or fluoroquinolone
  - Not recommended to use an aminoglycoside alone
  - Not recommended to use an aminoglycoside and fluoroquinolone combination
  - Use local biograms
  - Re-evaluate antibiotic choices at 42 and 72 hours with cultures and sensitivities and clinical response

- **Alternative treatment options for MDRPA**
  - Synergy with two and three drug combination; three \( \beta \)-lactams, two \( \beta \)-lactams plus amikacin, or \( \beta \)-lactam plus amikacin and ceftazidime
  - Colistin plus rifampin, or colistin plus tigecycline
  - Colistin: initial dose of 3.7-5mg/kg/day, monitor for nephrotoxicity and neurotoxicity
  - Polymyxin B: initial dose of 1.5-2.5 mg/kg/day, adjust for creatinine clearance
  - Aerosolized Inhaled Colistin Antibiotic for pneumonia: dose of 150 mg every 12 hours
APPENDIX B

Treatment Research Table
<table>
<thead>
<tr>
<th>Author</th>
<th>Objective</th>
<th>Methods</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Michel, F., et al. (2005)</td>
<td>Evaluate effectiveness of routine endotracheal aspirate cultures to treat VAP</td>
<td>299 patients total, 75 patients bronchoscopy and endotracheal cultures, 41 patients with VAP</td>
<td>Adequate antibiotics were prescribed in 95% of routine EA patients found to have VAP vs. 68% of adequate antibiotic treatment without routine EA cultures.</td>
</tr>
<tr>
<td>Kollef, Sherman, Ward, and Fraser (1999)</td>
<td>To evaluate differences in mortality associated with inappropriate initial antibiotic treatment</td>
<td>University hospital over 8 months 7/97-3/98. 655 total enrolled, 169 inadequate treatment 162(24.7%) with antibiotic resistant gram-negative bacteria</td>
<td>All cause mortality for inappropriate Antibiotics treatment vs. appropriate treatment (52.1%vs 23.5%) statistically significant Infection related mortality for inappropriate treatment vs. appropriate treatment (42% vs. 17.7%) Mortality for antibiotic resistant gram-negative infection 41.2% Common cause for inappropriate antibiotic treatment was resistant gm-negative infection.</td>
</tr>
<tr>
<td>Micek S., et al. (2005)</td>
<td>Importance of appropriate initial antibiotic treatment</td>
<td>305 patients over a 6 year period from 1/97-12/02.</td>
<td>Mortality for inappropriate initial antibiotic significantly higher than mortality for appropriate initial ABX (30.7% vs. 17.8%)</td>
</tr>
<tr>
<td>Koomanachai, Tiengrim, Kiratisin, Thamlikitkul (2007)</td>
<td>To determine safety of colistin</td>
<td>93 patients with MDR PA or A. Baumannii. Dose of 5mg/kg/day IV BID. 78 patients received colistin</td>
<td>80% clinical response 95% had microbiological response. 30% nephrotoxicity Mortality 46.2 in colistin group vs. 80% in non colistin group</td>
</tr>
</tbody>
</table>
| Maeda et al. (2008)          | Evaluate effects of antimicrobial drugs on strains of MDRPA               | Out of 1720 strains collect 4 were resistant to 8 antibiotic Susceptibility test by agar dilution | Colistin had most antimicrobial effects. 3 drug regimens were also effective. • Ceftazidime+aztreonam+ amikacin or
<table>
<thead>
<tr>
<th>Authors</th>
<th>Study Description</th>
<th>Results/Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sabuda D., et al. (2008)</td>
<td>Patients who received colistin between 1/00-12/05 in retrospective study for safety, route and response</td>
<td>28 courses of colistin by 22 patients, 12 received nebulized colistin, 12 received IV colistin. Favorable response in 67% with IV TX. 50% favorable response with INH. 56% nephrotoxicity. Average dose 3.7mg/kg/day, inhaled dose 150mg q12hr, suggested to use bronchodilator before dose.</td>
</tr>
<tr>
<td>Michalopoulos A., et al. (2005)</td>
<td>Collected information from 10/00 to 1/04. Looked at safety and response with aerosolized colistin for MDR gm negative bacteria</td>
<td>8 patients received aerosolized colistin. 6 of 8 patients had VAP with gm negative bacteria. All had concomitant IV ABX. Favorable outcomes in 7 out of 8 patients. Dose 1.5 to 6 million IU TID or QID average of 10 days. No adverse reactions such as bronchospasm or chest tightness.</td>
</tr>
<tr>
<td>Furtado G. et al. (2007)</td>
<td>Safety and response of treatment of MDRPA with polymyxin B</td>
<td>74 patients with HAP with MDRPA treated with polymyxin B as salvage therapy. Favorable outcomes 47.3% ARDS and sepsis independently associated with worsening symptoms or death.</td>
</tr>
<tr>
<td>Ostronoff et al. (2006)</td>
<td>Treatment of MDRPA in immunocompromised patients</td>
<td>2 case reports of patients on chemotherapy with MDRPA. Treatment with polymyxin B combined with Rifampin as synergistic therapy. 19 and 21 days course both with clinical and bacteriological cure.</td>
</tr>
</tbody>
</table>
VAP- ventilator acquired pneumonia, HAP hospital acquired pneumonia. Favorable outcomes are defined by clinical resolution of infection or cultural resolution of infection.

**Epidemiological Research Table**

<table>
<thead>
<tr>
<th>Author</th>
<th>Number of patients and cases</th>
<th>Epidemiology of Pseudomonas aeruginosa</th>
<th>Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yetkin G., Otlu B., Cicek A., Kuzucu C., and Durmaz R., (2006)</td>
<td>105 Pseudomonas strains identified among 80 inpatients in a 1-year period in a university hospital in Turkey</td>
<td>Underlying disease (48%), chronic illness (32%), and malignancy (20%). Urinary and/or other catheterization (71%). #1 Urinary tract infection (35%) was the most frequent infection encountered, #2 respiratory tract infection (34%) and #3 sepsis (13%)</td>
<td>Resistance to the antibiotics tested was in the 12% to 88% range, Amikacin was the most effective, Ceftriaxone was the least effective antibiotic</td>
</tr>
<tr>
<td>Noue´r S., Nucci M., de-Oliveira M., Pellegrino F., Moreira B., (2005)</td>
<td>Looked at 18 cases of spm- MRDPa, and used non spm-MRDPa as controls</td>
<td></td>
<td>Correlation with quinolones for spm MRDPa, Higher risk associated with history of antibiotics usage.</td>
</tr>
<tr>
<td>Gaynes , Edwards, and National Nosocomial Infections Surveillance System (2005)</td>
<td>From 1986 through 2003, data on 410,503 bacterial isolates associated with nosocomial infections were submitted from ICUs in NNIS hospitals.</td>
<td>Pseudomonas aeruginosa was responsible for: 18.1% Pneumonia, 3.4 % Blood stream infection (BSI), 9.5% of surgical site infection (SSI), 16.3 % Urinary tract infection (UTI)</td>
<td>Resistance patterns for Pseudomonas aeruginosa from 1986 to 2003 were statistically significant from 13% in 1986 to 23% in 2003.</td>
</tr>
<tr>
<td>Vonberg et al. (2008)</td>
<td>503 cases of multidrug-resistant gm-negative cases (MRGN) during 36months during</td>
<td>P. aeruginosa accounted for 202 of the 503 cases (40.2%)</td>
<td>Transmission of MRGN was 4.7% in this facility, 108 (21%) of the 503 were pan-resistant</td>
</tr>
<tr>
<td>Study</td>
<td>Methodology</td>
<td>Findings</td>
<td></td>
</tr>
<tr>
<td>------------------------------------</td>
<td>-----------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Izumida et al. (2007)</td>
<td>Used the Japanese National epidemiological surveillance of infectious diseases (NESID) 500 hospitals report From 2001-2005</td>
<td>Multidrug-resistant P. aeruginosa reports average 608-747 cases each year for 11-13%</td>
<td></td>
</tr>
<tr>
<td>Neuhauser et al. (2003)</td>
<td>Participating institutions, representing a total of 43 US states plus the District of Columbia, provided antibiotic susceptibility results for 35790 nonduplicate gram-negative aerobic isolates recovered from ICU patients between 1994 and 2000.</td>
<td><em>Pseudomonas aeruginosa</em> was the most frequent isolate from the respiratory tract (31.6%) and wounds (24.9%). <em>Pseudomonas aeruginosa</em> resistance to fluoroquinolone antibiotics increased from 23% to 29.5%</td>
<td></td>
</tr>
<tr>
<td>Shorr (2009)</td>
<td>Meta-analysis of with 21 original studies.</td>
<td>Gram-negative bacteria resistant increased the ICU mortality and costs</td>
<td></td>
</tr>
<tr>
<td>Pop-Vicas, Strom, Stanley, and D’Agata (2008)</td>
<td>Looked at gram-negative bacteria among patients who require chronic hemodylsis. 67 patients, 172 cultures from March 2005 to September 2005</td>
<td>Chronic hemodyalysis patients</td>
<td></td>
</tr>
<tr>
<td>Streit, Jones, Sader, &amp; Fritsche, (2004)</td>
<td>The SENTRY antimicrobial surveillance program. 25 ICUs in North America reported 1321 bacterial strains</td>
<td>Multidrug-Resistant gram-negative bacteria was 16%. Resistant rates for P. aeruginosa was from 3.1 to 24.8% ceftazidime 19.3% imipenem 16.1% ciprofloxacin 24.8%</td>
<td></td>
</tr>
<tr>
<td>----------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------</td>
<td>------------------------------------------</td>
<td></td>
</tr>
<tr>
<td><strong>References</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Koomanachai, P., Tiengrim, S., Kiratisin, P., Thamlikitkul, V., (2007) Efficacy and safety of colistin (colistimethate sodium) for therapy of infections caused by multidrug-resistance *Pseudomonas aeruginosa* and Acinetobacter baumannii in Siriraj hospital, Bangkok,


impact on empirical therapy. *Clinical Microbiology and Infectious Diseases, 14*(Suppl 6), 2-8.


