Assessment of Risk Factors for Multi-Drug Resistant Organisms to Guide Empiric Antibiotic Selection in Long Term Care: A Dilemma

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Multidrug-resistant organisms (MDRO) are a significant problem in many long-term care facilities (LTCFs), as well as hospitals. It is important that practitioners identify residents at risk for infection with MDROs. The risk factor assessment should be done before selecting empiric antibiotic therapy. It is well documented that during critical illness failure to “get it right the first time” with antibiotic therapy leads to excess mortality. The data for this conclusion come from studies of hospitalized patients that included identifying the etiologic organism in culture and documenting resistance by sensitivity testing. In clinical practice it is difficult to get cultures in LTCFs, especially in residents with pneumonia, and there will inevitably be a delay in obtaining the results, so empiric therapy must be given, and should consider risk factors for MDRO. If this is done, it may lead to more accurate antibiotic choices, and may prevent some patients with a mild-moderately severe infection from becoming severely ill as a consequence of inappropriate empiric therapy. The American Thoracic Society/Infectious Disease Society of America (ATS/IDSA) Clinical Practice Guideline for Health-Care Associated Pneumonia focused on patients ill enough to require hospital admission. It is unclear how this Guideline should be applied to residents with pneumonia who remain in the nursing home. The Guideline recommended performing a risk factor assessment for MDRO, combined with a low threshold for using empiric antibiotics directed at MDRO, along with efforts to culture the causative pathogen to allow “de-escalation” of antibiotic therapy. This approach can give the best of all worlds: appropriate and effective therapy, while limiting the duration of broad-spectrum therapy, a responsible strategy that could limit the selection of the next generation of MDRO pathogens.

RISK FACTOR ASSESSMENT: HOW TO DO IT

A number of studies demonstrate that a past medical history of infection/colonization with resistant gram-positive and gram-negative bacteria is a risk for subsequent infection with these pathogens. A systematic review of 10 observational studies by Safran and Bradley found that 26% of 379 subjects with methicillin-resistant Staphylococcus aureus (MRSA) colonization later developed infection (including 22% of 158 long-term care facility residents). Because sputum cultures are seldom performed in LTCFs, the burden of infection was probably greater. The risk of infection was 4 times greater for those colonized with MRSA versus those colonized with a sensitive S. aureus. A hospital-based study found that a past history of MRSA colonization or infection was predictive of MRSA bacteremia (odds ratio 4.05). In this study, 26% of 287 cases of MRSA bacteremia had MRSA isolated in prior cultures. A study by the Department of Veterans Affairs of 352 MRSA outpatient and inpatient infections found that a past history of MRSA infection increased the odds ratio of subsequent infection to 3.9. One report of 562 cases of MRSA bacteremia found that a history of prior infection with MRSA was not predictive of receipt of appropriate therapy, suggesting that clinicians may ignore or discount this risk factor when choosing empiric therapy. Perhaps the designation on many medical records “History of MRSA” has become so familiar that it has blended into the background, and is overlooked as a guide to therapy decisions.

Rising rates of gram-negative MDROs have been documented and, as in the case of MRSA, observational studies indicate that colonization with these organisms places the individual at increased risk for subsequent infection. As a result of rising rates of gram-negative resistance, previous “work horse” agents, such as quinolones, are no longer reliable empiric choices. O’Fallon et al analyzed 1661 clinical cultures obtained in a 750-bed LTCF over 2 years, documenting that the prevalence of ciprofloxacin-resistant gram-negative bacteria increased from approximately 7% in 2003 to 13% in 2005. These isolates were more common than MRSA. Pop-Vicas et al recovered 61 gram-negative MDRO from elderly bacteremic patients between 1999 and 2007. The
frequency of resistant isolates increased from 1% to 16% during this period. Rising rates of MDRO may partially invalidate the conclusions of older reports. Lautenbach et al\textsuperscript{16} identified 1805 gram-negative organisms in urine cultures obtained from residents of 63 LTCFs over 10 months in 2008, and found that the prevalence of fluoroquinolone resistance in \textit{Escherichia coli} was 51% (446 of 874 isolates). The prevalence of ceftazidime and imipenem resistance in \textit{Klebsiella} species was 26% and 6%, respectively (84 and 19 of 323 isolates). Ceftazidime resistance is a marker of the presence of extended spectrum beta-lactamase (ESBL) production, whereas imipenem resistance is a marker of carbapenemase production. The prevalence and patterns of resistance vary significantly by facility type, size, and location, with each institution having unique patterns. Therefore, it is essential to collect these data for your facility and not to assume that your facility’s problems are the same as those reported by others.

In assessing risk for infection with MDRO, it is important to consider facility-specific colonization rates of MDRO, to define the local “colonization pressure.”\textsuperscript{17–19} Each facility should maintain a bacteriology database sorted by nursing unit, organism, antibiotic sensitivity, and date.\textsuperscript{20} Isolates obtained following transfer to the emergency room or during the first 2 to 3 days following hospital transfer are considered to be LTCF acquired if there was no past medical history of isolation\textsuperscript{17,20}; however, it may be difficult to determine with certainty if initial colonization occurred in a hospital or LTCF. The bacteriology database may also help the LTCF by identifying any clusters of facility-acquired MDRO in time/space (evidence of transmission). Genetic testing could also be performed to verify strain relatedness.\textsuperscript{20} The database can also be used to determine the facility’s burden of MDRO such as the percentage of quinolone-resistant organisms in urinary isolates and in “quality” sputum isolates or the percentage of all \textit{S. aureus} isolates with methicillin resistance.\textsuperscript{21}

In this analysis, only one isolate of a given type from the same resident should be included.\textsuperscript{16} Admittedly, percentage of MDRO isolates from a clinical bacteriology database is not the same as percentage of MDRO colonization from screening asymptomatic residents. However, both determinations reflect the facility burden of MDRO. This information can assist clinicians in selecting empiric antibiotic therapy. Other facility-level risk factors include staffing levels, quality of care, and architectural design features such as sinks and private rooms.\textsuperscript{22} The assessment of facility-level risk factors can focus facility-level quality improvement efforts, and improve the prognosis of some residents.

In the assessment of patient risk, it is important to consider a history of recent antibiotic use, since such therapy may induce the overgrowth or emergence of MDRO.\textsuperscript{23,24} For example, Drinka and collaborators\textsuperscript{25,26} demonstrated that quinolone use was associated with increased risk of MRSA at both the individual and facility levels. The ATS/ISDA Clinical Practice Guideline for Community-Acquired Pneumonia recommend that if an antibiotic has been administered in the preceding 3 months, then an antibiotic from another class should be chosen as empiric therapy.\textsuperscript{27} Patients often remain colonized with MDRO for more than 3 months.\textsuperscript{11,28–30}

Given that our choice of antibiotic classes is limited, the ATS/ISDA Clinical Practice Guideline for Health Care—Associated Pneumonia allows a shorter period between use of antibiotics in the same class.\textsuperscript{1} Clinicians often fail to review recent antibiotic use or previous isolation of MDRO when choosing empiric therapy.\textsuperscript{10}

Most investigations of risk factors for MDRO have been hospital based and focused on individual risk factors. These studies identified residence in a LTCF as a powerful risk factor for MDRO infection\textsuperscript{9,12,15,31}; therefore, some hospitals screen all admissions from LTCFs for MDRO. Other individual risk factors include prior hospitalization, wounds, invasive devices, and comorbidity/need for contact care.\textsuperscript{15,31} Three groups of investigators have defined risk factor profiles for MDRO pneumonia in hospitalized patients to assist clinicians choosing empiric therapy.\textsuperscript{32–34} None considered “colonization pressure” or an individual history of MDRO in their assessments. El-Solh et al\textsuperscript{33} studied intubated residents, excluding those hospitalized in the preceding 6 months. An activity of daily living (ADL) dependency score of greater than or equal to 12.5 and antibiotic therapy within 6 months were identified as risk factors for MDROs. Shorr et al\textsuperscript{32} studied patients with health care—associated pneumonia. These authors had no information on recent antibiotic therapy. Hospitalization within 3 months (odds ratio [OR] 4.21), residence in an LTCF (OR 2.75), long-term hemodialysis (OR 2.11), and ICU admission/illness severity (OR 1.62) were risk factors for MDROs. Finally, Brito and Niederman\textsuperscript{34} performed a literature review. Illness severity, antibiotic therapy within 6 months, hospitalization within 3 months, and ADL dependency were identified as risk factors for MDROs.\textsuperscript{32–34}

Some risk factors have more importance than others, but this concept needs further exploration.\textsuperscript{31,32} We recommend that clinicians be mindful of the risk factors listed in Table 1 during the implementation of empiric therapy. If the resident fails to respond to initial empiric therapy (treatment failure), then the clinician must consider several possibilities including alternate noninfectious diagnoses, recurrent aspiration, biofilm formation, abscess, metastatic infection, or pathogens not “covered” by current antibiotic therapy.

### Table 1. Risk Factors for Multidrug-Resistant Organisms\textsuperscript{13,17–19,26,27,31–35}

<table>
<thead>
<tr>
<th>EXPOSURE</th>
<th>History of MDRO</th>
<th>Colonization pressure (facility rates of MDRO infection/colonization)</th>
<th>Recent antibiotics</th>
<th>Recent hospitalization</th>
<th>Comorbidity/Dependency (need for contact care)</th>
<th>Dialysis</th>
<th>“FERTILE GROUND” FOR BACTERIAL PROLIFERATION</th>
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<tbody>
<tr>
<td>Wounds</td>
<td>Indwelling devices</td>
<td>Dental plaque</td>
<td>Structural lung disease/bronchiectasis, COPD (Pseudomonas)</td>
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COPD, chronic obstructive pulmonary disease; MDRO, multidrug-resistant organisms.
including MDRO and Legionella. We divide the risk factors into 2 categories: “exposure” to antibiotics and MDRO in the environment and “fertile ground” conditions that facilitate colonization and infection. It is unclear if severe illness alone actually increases the risk of MDROs; however, patients with severe illness should generally have a lower threshold for MDRO coverage because failure to adequately treat these patients will increase mortality, without an opportunity to correct mistakes later. Good patient data are required during hospital transfer to identify at-risk individuals to the hospital, so this information can be used to guide initial therapy.

DILEMMAS

Although pneumonia is a common and deadly infection in residents of LTCFs, it is usually treated empirically without isolation of the causative organism. Some patients may have viral or nonbacterial “pneumonitis” that does not require antibiotic therapy. Aspiration pneumonitis classically follows large bolus gastric aspiration of food, acid, or digestive enzymes and is initially noninfectious if the stomach is not colonized with bacteria. Large bolus gastric aspiration events may have an acute/dramatic onset and occur when the resident is laying flat (with vomit on the pillow) or may be witnessed by staff after a meal. Most residents with this clinical picture receive antibiotic therapy. The best data on the bacteriology of aspiration pneumonia in LTCF residents treated with mechanical ventilation comes from El-Solh et al. Protected broncho-alveolar lavage was performed within 4 hours of admission in 95 residents with risk factors for pharyngeal aspiration or regurgitation. In 41, clinicians failed to isolate bacteria (10 colony-forming units/mL). These patients may have had a nonbacterial pneumonitis (acid, enzymes, food). If patients with nonbacterial aspiration are treated, and really do not need antibiotics, then their improvement may be attributed to antibiotic therapy, and give clinicians a misleading impression that the antibiotic treatment was beneficial. Unfortunately, there is no gold standard to define nonbacterial aspiration pneumonitis, and even the use of biomarkers has fallen short in distinguishing bacterial aspiration pneumonia from aspiration pneumonitis. Risk factor assessment will not precisely determine which residents with nursing home—acquired pneumonia require treatment for nosocomial pathogens. Previous reports indicate that “nosocomial” coverage may not be necessary for many residents. A nonrandomized retrospective study of 334 hospitalized residents with pneumonia found no significant difference in mortality or time to clinical stability in 76 “covered” with antibiotics targeted to “nosocomial” pathogens versus 258 treated with antibiotics targeted to “community” pathogens. The study excluded residents with certain risk factors for MDRO, including those who received more than 1 dose of antibiotic before admission, required care in the ICU, or had a history of recent hospitalization (1 month). In addition, reports generated thru 2005 indicate that quinolones and ceftriaxone have been effective in nursing home—acquired pneumonia.

Currently many residents with guarded prognosis receive empiric antibiotic therapy in the LTCF, and in our view, many of the conditions that put these residents at risk for MDROs are the same conditions that can lead to a “guarded” prognosis and to a directive of “do not hospitalize.” It is important to understand that antibiotics should not be viewed as a “harmless,” end-of-life therapy, provided to patients out of a desire to “do something, rather than nothing.” We should carefully consider if we are using a therapy in patients who will benefit. Antibiotic treatment of severely debilitated residents with ongoing recurrent aspiration and/or biofilm formation may not be beneficial. Lack of benefit may be related to infection caused by MDRO induced by previous antibiotic exposure. D’Agata and Mitchell followed 214 residents with advanced dementia for an average of 322 days. Two thirds received antibiotics. The mean number of courses administered to those residents was 4.

Unfortunately we have very little information about the bacteriology of aspiration syndromes in debilitated residents treated in the nursing home. We are concerned that in some facilities the bacteriology in this group may be similar to hospitalized residents, associated with loss of quinolone and ceftriaxone efficacy. Therefore, we need updated and accurate MDRO risk factor assessment for nursing home residents based on better diagnostic information including culture of the causative pathogen. Cultures will also allow “de-escalation” of antibiotic therapy. Without such information, MDRO risk factor assessment will paradoxically lead to greater antibiotic coverage of “nosocomial” pathogens, greater antibiotic pressure, and the emergence of a new generation of MDROs in the resident and the entire facility. Therefore, the use of antibiotics directed at MDROs should be selective.

SOLUTIONS

At this time we can explain to residents/surrogates that antibiotic use selects resistant bacteria in the individual as well as the entire facility. Antibiotics may be withheld with informed consent if their use is futile, death is inevitable/imminent because of an untreatable progressive process, or if potential adverse effects outweigh individual benefit (side effects, induction of resistance in the individual, or prolongation of suffering and the dying process). Obtaining such a directive is labor intensive and can generally be obtained only by a trusted practitioner. A hospice referral might facilitate such a directive. A 2004 publication in the Journal of the American Medical Association presented a Minimum Data Set—based assessment designed to predict 6-month mortality in advanced dementia. Withholding antibiotics must be accompanied by effective comfort measures. Given the current regulatory and legal environment, practitioners are expected to maximize individual resident outcomes and autonomy. Practitioners are not empowered to “ration” individual antibiotic coverage for nosocomial pathogens based on potential harm to the community. Transparency and societal agreement by political and public health authorities would be required to resolve this dilemma.
The risk factor assessment for MDROs can serve as a springboard for a multifaceted program to limit the impact of MDRO. The reader is encouraged to consult current Clinical Practice Guidelines for pneumonia- and catheter-associated urinary tract infection (UTI) that generally recommend limiting the duration of antibiotic therapy to 7 days for infected patients who have a good response with resolution of clinical features of infection. In the case of pneumonia, a longer course of treatment is recommended with tissue necrosis and for organisms such as Pseudomonas.1,2,7,48 Drinka and collaborators50 previously provided readers of this Journal with a number of approaches including restricting antibiotic use for UTI to residents with urinary signs/symptoms or evidence of a systemic infectious illness (fever, leukocytosis), recognizing and preventing large bolus gastric aspiration events with rapid discontinuation of antibiotic therapy if the resident’s illness rapidly resolves, limiting the impact of “fertile ground” with wound care programs, dental hygiene, and discontinuation/proper care of invasive devices and good standard secretion containment.35,49–51

If the pathogen is not isolated to allow de-escalation of broad-spectrum antibiotic therapy, the use of risk factor assessment to choose empiric therapy (without overusing antibiotics) remains a dilemma.

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