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Colonization with Multi-Drug Resistant Organisms in Nursing Homes: Scope, Importance, and Management

Marco Cassone, MD, PhD[1] and **Lona Mody, MD, MSc**[1,2,*]

[1]Division of Geriatric and Palliative Care Medicine, University of Michigan Medical School, Ann Arbor, MI

[2]Geriatrics Research Education and Clinical Center (GRECC), Veteran Affairs Ann Arbor Healthcare System, 11-G GRECC, 2215 Fuller Rd., Ann Arbor, MI 48105, US

Abstract

Bacterial infections are among the most common causes of morbidity and mortality in Nursing Homes (NH) and other long term care facilities. Multi-drug resistant organisms (MDROs) represent an ever-increasing share of causative agents of infection, and their prevalence in NHs is now just as high as in acute-care facilities, or even higher. Indeed, NHs are now considered a major reservoir of MDROs for the community at large. Asymptomatic colonization is usually a prerequisite to development of symptomatic infection. While progress has been made in defining epidemiology of MDROs in NHs, few studies have evaluated the role of changing healthcare delivery in introducing and further transmitting MDROs in this setting. Furthermore, the factors influencing the spread of colonization and the key prognostic indicators leading to symptomatic infections in the burgeoning short stay population need to be explored further. The difficulty of this task lies in the heterogeneity of NHs in terms of focus of care, organization and resources, and on the diversity among the many MDRO species encountered, which harbor different resistance genes and with a different prevalence depending on the geographic location, local antimicrobial pressure and residents risk factors such as use of indwelling devices, functional disability, wounds and other comorbidities. We present literature findings on the scope and importance of colonization as a pathway to infection with MDROs in NHs, underline important open questions that need further research, and discuss the strength of the evidence for current and proposed screening, prevention, and management interventions.

Keywords

Nursing Home; Multi-Drug Resistant; Colonization; VRE; MRSA; Geriatric

Lona Mody, MD, M.Sc, University of Michigan Medical School, Division of Geriatric and Palliative Care Medicine, 300 N. Ingalls Rd., Rm. 905, Ann Arbor, MI 48109, Tel: 734-764-8942, Fax: 734-936-2116 lonamody@umich.edu.

Conflict of Interest

Marco Cassone and Lona Mody declare that they have no conflict of interest.

Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Introduction

Infections remain the most commonly diagnosed conditions in the United States, including hospitals and Nursing Homes (NHs) [1]. In the United States and many other countries, there are more residents in Nursing Homes (NHs) than in acute care hospitals, and infection is one of the top five causes of death [2, 3] and probably the first among preventable causes. Indeed, NH residents are more likely to receive antibiotics at least once, than any other individual class of drugs [4]. Bacterial infections are more frequent than viral, fungal or protozoan infections in older adults, and they are often preceded by skin or mucosal colonization for a variable length of time. Urinary tract infections, lower respiratory tract infections, gastroenteritis (including viral and bacterial etiologies), and skin and soft tissue infections are the most common infections affecting NH residents. Diagnosis is often problematic because older adults may not mount an adequate fever response and generally show nonspecific signs and symptoms. Also, sampling difficulties and limited timely access to laboratory tests may lead to prolonged administration of empirical antibiotic therapy. These factors lead to overuse of antibiotics, which remains widespread, and stems from diagnostic uncertainty especially in frail older adults with multiple comorbidities, difficulty in predicting severity of infections and a preference for broad-spectrum antibiotic regimens even when they are unnecessary.

Over 35% of NHs residents are colonized with multi-drug resistant organisms (MDROs) [5–13]. When infections with MDROs develop in older adults, intolerance and interactions involving specific classes of antibiotics can further reduce viable therapeutic options. In this paper, we discuss the prevalence of selected MDROs in NHs when compared with other healthcare settings, and we illustrate the risk factors of colonization with MDROs in NH residents and its importance in terms of adverse outcomes. We then focus on NHs as an ideal environment to further our knowledge of colonization pathways and duration, a key but still underappreciated topic of investigation, and discuss prevention and management strategies.

Nursing Homes and the changing epidemiology of antimicrobial resistance

NHs are at the very center of antimicrobial resistance concerns. Of the 18 top antibiotic resistant threats identified by the Centers for Disease Control and prevention (CDC) in 2013 [14], at least 11 are especially relevant to NH residents. These are listed in Table 1. The antimicrobial-resistant bacteria responsible for most morbidity and mortality in NHs, and which have been most studied from an epidemiological point of view, are methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant Enterococci (VRE), and multi-drug resistant Gram-negative bacilli (MDR-GNB), defined as resistant to three or more antibiotic classes. Among MDR-GNB, the most common species are *Escherichia coli, Klebsiella pneumoniae, Proteus, Acinetobacter baumanii, Pseudomonas aeruginosa* [9]. Less frequently encountered species, such as *Stenotrophomonas maltophilia* and *Burkholderia cepacia* are also important because they are commonly resistant to many broad-spectrum antibiotics [15].

Methicillin-resistant Staphylococcus aureus

Invasive MRSA infections are common in all institutional and community settings, and their incidence in the US is 25 cases per 100,000, and a mortality of 3.5 per 100,000 in one study [16••]. MRSA has become the most common agent of community-acquired skin and soft tissue infections [17]. Almost half of all *Staphyloccoccus aureus* clinical isolates in the US are resistant to methicillin, and many other countries in the world, including Western and Southern Europe, report similar prevalence rates of resistance [18••, 19]. MRSA are resistant to most beta-lactams and often fluoroquinolones, macrolides, aminoglycosides and other classes of antibiotics, leaving only a few therapeutic options, most commonly glycopeptides [20]. Low level glycopeptide-resistance is emerging, especially in heterogeneous vancomycin-intermediate *S. aureus* (hVISA) infections [21], which often necessitates a switch to suboptimal alternative treatment regimens. In NH studies conducted in different regions within the US, the prevalence of MRSA among *S. aureus* isolates hovers around 30%, but can be as high as 60%. 8 to 10% of all NH residents are colonized with MRSA ([8•, 11, 22–25]. The likelihood of acquiring new MRSA colonization may be greatly influenced by the type of care received. For example, in a recent study, NH residents in rehabilitation care were four times as likely to acquire MRSA than those in residential care, and showed some differences in the relative importance of specific risk factors, such as previous antibiotic treatment and being bedbound [26].

Vancomycin-resistant enterococci

Antimicrobial resistance in enterococci is another important public health issue, although not entirely new, since they are intrinsically insensitive to many antibiotics. Enterococci are responsible for a significant number of infections in hospitalized older adults ranging from urinary to wound infections and endocarditis. Many risk factors for VRE colonization have been established, including severe renal and hematologic diseases, malignancies, organ transplants, presence of invasive devices, prior antibiotic treatment, and proximity/interaction with other colonized individuals. Most of these factors are more likely to be present with advanced age. Also, specific risk factors allowing colonizing enterococci to establish life-threatening systemic infections, such as presence of valvular heart defects or indwelling urinary catheters, are typically found often in older adults. The prevalence of VRE among all enterococci in US care institutions is around 33%, while in Europe it ranges from <2% (Finland, Holland) to >20% (Ireland, Greece, Portugal) [27]. In US NHs, the prevalence ranges between 5 to 18% [8•, 28], but can be as high as 50% in certain institutions [29] often due to a high likelihood of patient-to-patient transmission and inter-institution transfer [30]. One of the few alternative therapies to vancomycin, synergistic combinations of beta-lactams and aminoglycosides, is concurrently losing efficacy due to an increase in high-level amionoglycoside resistance [31, 32]. It has been well established that vancomycin resistance increases the associated mortality rate of enterococcal infections by at least twofold [33].

Multi-drug resistant Gram-negative bacilli

The rates of MDR in healthcare-associated infections vary across species. For example, among patients and residents of hospitals and other healthcare centers in the US, 15% of *K.*

pneumoniae or *K. oxytoca* and 65% of *A. baumannii* clinical isolates are resistant to three or more different classes of antibiotics, thus meeting MDR-GNB criteria [18••]. Resistance to third-generation cephalosporins is also concerning (> 25% in *Enterobacter* and *Klebsiella*, > 15% in *E. coli*). Resistance is also on the rise in Europe, where the 29-Country European Antimicrobial Resistance Surveillance System network reported a general increase of antimicrobial resistance in *E. coli*, *K. pneumoniae* and *P. aeruginosa* [34]. Up to 36% of *E. coli* isolates were resistant to third-generation cephalosporins. 15.3% of *P. aeruginosa* and 22.3 % of *K. pneumoniae* isolates were MDR. Notably, in Europe there is extreme geographic variability with low rates of resistance across most of the North, especially in Scandinavian countries, and an increasing gradient of resistance towards the South and East. Several Southern and Eastern European Countries now report more than 50% of *K. pneumoniae* and *P. aeruginosa* as MDR, and between 25 and 50% of *E. coli* [35••]. Carbapenem resistance in *E.coli* is still negligible rates across the continent, however this organism has at least a 10% resistance rate to fluoroquinolones everywhere.

Beta-lactam and carbapenem resistance in *K. pneumoniae* and fluoroquinolone resistance in *E. coli* and *Proteus* are especially of concern. Resistance to fluoroquinolones such as ciprofloxacin is becoming common in the US as well as in most of Europe and Asia. As a result, the therapeutic guidelines of such common infections as pneumonia, gastroenteritis and urinary tract infections are undergoing major modifications. However, it is difficult to match the bio-distribution, spectrum of activity, and safety in adults that fluoroquinolones offer with other oral agents, and concerns about a new “post-quinolone era” and its’ challenges have begun already [36].

NH residents are also an important reservoir of MDR-GNB. The prevalence and resistance patterns vary greatly depending on type and location of the facility [37] with prevalence rates averaging around 20% [38], but as high as 50% or more in some institutions. Resident-to-resident spread has been demonstrated [9, 11, 25, 37, 39, 40]. Focusing on residents with established risk factors uncovers worrisome trends: Fisch et al observed a prevalence of ciprofloxacin resistance of > 50% in NH residents with indwelling devices [8•].

Data on individual organisms, their susceptibility patterns and mechanism of resistance is not widely available for NHs, but studies point to a significant prevalence of antimicrobial resistance in this institutional environment [41]. The latest PanEuropean Survey of antimicrobial resistance in NHs [42] showed that, among the isolates with confirmed antimicrobial susceptibility data, resistance to third-generation cephalosporins hovers around 20% for *E. coli* and *Klebsiella* and around 30% for Proteus. Additionally, 24% of *P. aeruginosa* isolates were carbapenem-resistant or intermediate.

Risk factors—With this changing epidemiology, the burden of antimicrobial resistance has reached the critical mass for spreading independently of antibiotic treatment, thus complicating targeted prevention efforts. Twenty or so years ago investigations of epidemics of MDROs in NHs would likely have shown incoming carriers from acute-care facilities as index cases or “case zero” for MDROs [43]. Presently, NHs and other long-term care facilities have become a reservoir for MDROs. Numerous studies report a recent residence in a NH as an independent risk factor for colonization with MDROs [44–46]. A systematic

meta-analysis of factors associated with MRSA colonization at time of hospital admission in 77,000 patients showed that recent NH exposure was at least as important as recent hospitalization (odds ratio 3.8, 95% confidence interval (CI), 2.3–6.3 for NH exposure versus 2.4,95% CI, 1.3–4.7 for hospitalization)[44].

Many risk factors for colonization with MRSA, VRE and MDR-GNB in NHs are common, despite substantial physiological differences between these organisms (Table 2) [44, 47, 48•]. The presence of devices such as urinary catheters or feeding tubes is a common risk factor, and it has been estimated that more than 50% of NH residents with indwelling devices are colonized with an MDRO [9, 10}. Lower functional status score is another very important common risk factor, which may be explained by the fact that residents who are less independent have more frequent contact with health care workers and therefore more opportunities for acquisition of antibiotic-resistant organisms [8, 9, 49, 50]. Other important general risk factors are pressure ulcers and wounds, urinary incontinence, and the presence of comorbidities [49, 51]. Previous antimicrobial therapy is an especially important risk factor for VRE colonization, with risk varying depending on the antibiotic received. Prior hospitalization is a general risk factor, as is current residence in a NH, again attesting to the changing epidemiology of MDROs and the important role of NHs [44, 48•]. In a study of an acute-care hospital in NYC and its associated long-term care facility, isolates from residents undergoing rehabilitation at the long-term care facility after being discharged from the hospital had a higher percentage of antimicrobial resistance than those from patients in the hospital [45]. The most relevant increases in resistance among isolates from long-term facility residents, were observed in enterococci (vancomycin resistance), staphylococci (methicillin resistance) and also in many Gram-negative species (especially resistance to new-generation fluoroquinolones, carbapenems, and antipseudomonal penicillins). Other risk factors that have been well established in multiple studies are: prior colonization by antibiotic-resistant organisms, male sex, need for high-intensity nursing care, older age, skin breakdown, and lower cognitive status [48•, 52]. The importance of comorbidities as risk factors varies depending on the organism; for example, diabetes mellitus and solid cancer are important risk factors for MDR *K. pneumoniae*. For MRSA, congestive heart failure, diabetes, pulmonary disease, and renal failure are important risk factors. Interestingly, in a recent study frequent social interaction among residents appeared to be protective of MRSA transmission, suggesting that residents healthy enough to engage in group activities do not incur substantial risks of MRSA from social contact [13].

Public Health importance and the prognostic role of colonization

Assessing and managing the burden of MDR bacteria in health care settings is universally recognized as a mean to improve public health. Screening for MRSA in high-risk residents, for example, is a legislative mandate in some US States [44]. NHs are perhaps the most important reservoir of MDR bacteria, but how much does this high burden of antimicrobial resistance directly affect health outcomes in older adults? MDR colonization significantly increases the risk of MDR infection, with relative risks ranging from 3 to 26 [5, 53–58]. Ruscher et al [59] recently found that most MRSA and MDR-GNB persistently colonized residents up to six months or more. Notably, in many cases infections tend to occur more often in residents colonized by resistant pathogens. Muder et al. showed that 25% of

rehabilitation and long-term-care residents colonized with MRSA developed MRSA infections compared to 4% of those not colonized with MRSA [55]. Despite some earlier literature linking MDR infections to an increase in mortality in at least certain scenarios and in the short term [60, 61], the majority of observations failed to show significant changes in long term all-cause mortality [62]; in a study focusing on colonization by MRSA and ESBL-producing GNB, colonization did not increase mortality or morbidity as assessed after 12 months [63]. Lee et al. used a mathematical model to predict that use of contact precautions for all MRSA carriers would reduce prevalence of MRSA, but they did not anticipate changes in clinical outcome [64]. In a recent study, mortality in a cohort of older adults hospitalized because of infection acquired in NHs versus in their home was similar, despite a significantly higher percentage of resistance among strains responsible for NH-acquired infections [65]. In the case of VRE however, once systemic infection is established, a clear jump in mortality occurs compared to susceptible enterococci [33].

Prevention and Management

Strategies to curb MDROs in NHs include antibiotic stewardship, standard precautions, education of healthcare workers (HCWs) and feedback, as well as active surveillance for infections [66–68••]. Additionally, modified contact precautions are recommended for residents with suspected or known infections by epidemiologically important organisms.

Reduction of antibiotic use in NHs can be accomplished first and foremost by the use of standardized definitions of infections, in order to reserve therapy in cases when the diagnosis of infection is confirmed or very likely. In particular, use of Loeb's minimum criteria for diagnosis of infection should be utilized to help achieve this goal [69]. Additionally, innovative educational strategies should be used to inform prescribing physicians about current recommended antibiotic therapy regimens in order to promote appropriate use of antimicrobials [70]. Empiric therapy should be switched to pathogen-tailored once culture data becomes available. Durations of antimicrobial therapy should be minimized whenever it can be done safely. Use of empirical and prophylactic antibiotics remains high and varies by geographic location. For example, it has been shown that empirical and prophylactic uses together account for 80% of all treatments in European NHs [71]. In a report by Latour and colleagues, empirical treatments were most common (54% of all antimicrobial therapies), followed by prophylactic (29%). Only a minority of treatment regimens were microbiologically documented (16%). While prescribing practices varied widely across countries, the authors identified conditions common to most countries for which antibiotic prophylaxis should be reduced, among which bacteriuria was the most important

Standard precautions must be used every time there is possibility that a HCW or other residents or patients may have contact with any body fluid, mucosae, or non-intact skin. These include hand hygiene, use of gloves, masks, eye protection, gowns, and correct technique/tools for managing and disposing of needles and other sharps [66]. A focus on HCW hand hygiene remains important. Mody et al showed that 65% of HCWs in NHs carry GNB on their hands [72]. McBryde et al showed in a hospital setting that 9–25% of HCWs gloves become contaminated with MRSA after care of a colonized patient [12]. Staff

education remains a critical step in infection prevention, in order to enhance adherence to proven infection prevention practices such as hand hygiene. Education can be provided using informal and interactive educational sessions, infection control walking rounds and huddles, as well as quality improvement initiatives and meetings, all coordinated by a dedicated infection preventionist with leadership support. Adherence among HCWs improves when protocols take workload and practical needs into account. A typical example is the introduction of the alcohol-based hand rub, which allows more frequent hand hygiene in less time than hand washing with water and soap, and limits skin irritation [72]. Also, hand hygiene with alcohol rub can be performed “on the go” and dispensers can be made ubiquitously available at strategic points and in the corridors.

Active surveillance for asymptomatic colonization involves screening of residents and the environment for MDROs, as opposed to passive surveillance which is based on the collection of data of clinical cultures. Active surveillance screening, followed by feedback to HCWs, frontline clinical staff, and leadership can be a powerful epidemiological and educational tool. Its cost-effectiveness depends on establishing specific procedures focused on the locally prevalent pathogens. In the case of MRSA, for example, the choice of body sites to screen is extremely important. The nares has been considered as the most common reservoir for MRSA, and thus often it is only site screened. In a recent study it was found that screening a number of additional body sites can more than double the sensitivity of the screening for MRSA [73•]. Not enough is known about which body sites are most frequently involved in transmission of MDROs to other residents, health care workers, and visitors. Little is also known regarding the relative likelihood of colonization leading to overt infection. Some of these questions may be better answered with the use of highly discriminatory molecular typing methods allowing for accurate tracking of organism spread at the single isolate level, rather than by clone.

One active surveillance strategy would be to focus on residents at high risk for infection and screen them for all the most relevant MDROs, rather than focus on a single MDRO [22]. When repeated over time, active screening can also be invaluable in establishing which colonization events are transient and which are persistent, as defined by two or more positive cultures separated by fewer than two negative cultures [55]. NHs offer a suitable environment to assess the outcomes of residents with persistent colonization because they allow extended follow-up. This is especially important since persistent colonization has a much higher likelihood to lead to adverse outcome than transient colonization. In the case of MRSA, persistent colonization is often linked to specific clonal strain types [55].

Additional precautions may be required during outbreaks in healthcare settings. For example, eradication of MRSA nasal carriage using mupirocin is advocated by some during outbreaks, and isolation of colonized residents may be required during VRE outbreaks [74, 75]. For MDR-GNBs the recommendations vary across species. This variability is mostly due to availability of scientific evidence for each species, rather than their different characteristics and epidemiology of the pathogens. The current recommendations from the European Society for Clinical Microbiology and Infection [76•] are presented in Table 3 (limited to recommendations with an emphasis degree of “Strong”).

As is clearly evident, some of the most effective control measures cannot be easily implemented in NHs. Isolation of the resident can be impractical, especially when more than 30% of all NH residents harbor an MDRO. Even strategies that don't require interfering with resident needs, such as antimicrobial stewardship, education and enforcement of contact precaution, require dedicated time and/or personnel, and perseverance and commitment by the residents, their families, frontline staff and leadership. In many cases it has been observed that help from specialized personnel from outside institutions (academic and/or infection control reference centers or consultants) for counseling and education improves outcomes. Some interventions have included establishment of a task-force with the autonomy to alter procedures and protocols as necessary [77]. Outside consultants however, cannot be consistently hired, for economic reasons. Thus, improving and streamlining awareness and control of MDROs within NHs often requires specific, tailored approaches focusing on proven cost-effective measures.

Conclusions

Antimicrobial resistance is now a worldwide phenomenon involving most pathogens and sparing no antibiotic. Its diffusion in the community outside of acute care facilities poses screening and management problems. NHs have a particularly high prevalence of MDROs, but because they are very heterogeneous in terms of resident characteristics and support/rehabilitation programs offered, the specific burden of each pathogen and its antimicrobial resistance spectrum varies. For this reason many MDRO screening and management strategies need to be tailored at the facility level.

Most risk factors for colonization and/or infection with MDROs in older adults are difficult to modify. However, antimicrobial use, which has been proven to be one of the most important risk factors, can be greatly reduced through appropriate antimicrobial stewardship programs. For prognostic and epidemiologic purposes, it is important to differentiate between persistent and transient colonization. Persistent colonization with MDROs has a much more important impact on the likelihood of infection and is more likely to spread than transient colonization. The two pillars of any strategy aimed at decreasing the prevalence of MDROs remain limiting the development of resistance by reducing antibiotic pressure and limiting the spread of resistant pathogens already in circulation through wide and conscientious adoption of evidence based infection prevention methods. The success of these two strategies depends on proper education and commitment of workers and decision-makers in NHs as we all as throughout the the wide spectrum of healthcare-related professions.

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Table 1

Top antibiotic resistance threats in NHs[a]

Organism	Est. hospitalizations[b] per year	Est. deaths per year	Primary Drug Resistance concern
Concern level			
URGENT			
Clostridium difficile	250,000	14,000	Fluoroquinolones
Carbapenem-Resistant Enterobacteriaceae	9,000	600	Carbapenems
SERIOUS			
Multidrug-Resistant *Acinetobacter*	12,000	500	Three or more classes
Fluconazole-Resistant *Candida*	10,000[c]	3,400	Azoles
Extended Spectrum β-Lactamase (ESBL)-Producing Enterobacteriaceae	26,000	1,700	Beta-lactams, cephalosporins
Vancomycin-Resistant *Enterococcus*	20,000	1,300	Glycopeptides
Multidrug-Resistant *Pseudomonas aeruginosa*	6,700	440	Three or more classes
Methicillin-Resistant *Staphylococcus aureus* (MRSA)	80,000	11,000	Beta-lactams, cephalosporins
Drug-Resistant *Streptococcus pneumoniae*	19,000	7,900	Beta-lactams, cephalosporins, macrolides
Drug-Resistant Tuberculosis	~150		Two major drugs or one major and two minor
CONCERNING			
Vancomycin-Resistant *Staphylococcus aureus* (VRSA)	~1		Glycopeptides

[a] Selected from the Center for Disease Control and Prevention's Antibiotic Resistance Threats In The United States, 2013 [14]

[b] includes prolonged hospitalizations

[c] only includes infections leading to sepsis

Table 2

Common and specific risk factors for colonization with selected MDROs in LTCFs, as confirmed by studies using multivariable analysis [44, 47, 48•].

Common	MDR-GNB	MRSA	VRE
• functional disability • presence of wounds • presence of urinary catheters • prior antibiotic therapy	• long stay, advanced age, large facilities • prior colonization • presence of feeding tubes • bladder dysfunction, fecal incontinence • pressure ulcers • comorbid conditions such as diabetes, cancer, renal disease, inflammatory bowel disease	• long stay, advanced age, male sex • low cognitive status • prior colonization • prior hospitalization • presence of feeding tubes or intravenous central catheters • urinary incontinence • pressure ulcers • comorbid conditions such as diabetes, pulmonary disease, heart failure	• prior hospitalization • proximity to other colonized individuals • presence of feeding tubes

Table 3

ESCMID recommendations for containment of selected MDR- gram negative bacteria. Strongly recommended measures in endemic and in outbreak situations and level of evidence [76•]

	ESBL-producing Enterobacteriaceae		**MDR-*Klebsiella pneumoniae***		**MDR-*Pseudomonas aeruginosa***		**MDR-*Acinetobacter baumannii***	
	Endemic	**Outbreak**	**Endemic**	**Outbreak**	**Endemic**	**Outbreak**	**Endemic**	**Outbreak**
Hand Hygiene	***	***	***	*	***	*	***	***
Contact Precaution	***	***	***	***	***	*	***	***
Antimicrobial Stewardship	***	***						
Isolation Room		***	***	***		**	***	**
Alert Code		***		***			***	
Education		***					***	
Environmental Cleaning		***					***	***
Active Screening Cultures		***		***		*		***
Cohort Residents				***				
Cohort Staff				***				

Level of Evidence for Recommendation:

* very low,

** low,

*** moderate