

Nutritional Strategies to Boost Immunity and Prevent Infection in Elderly Individuals

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Older adults are at risk for malnutrition, which may contribute to their increased risk of infection. Nutritional supplementation strategies can reduce this risk and reverse some of the immune dysfunction associated with advanced age. This review discusses nutritional interventions that have been examined in clinical trials of older adults. The data support use of a daily multivitamin or trace-mineral supplement that includes zinc (elemental zinc, >20 mg/day) and selenium (100 µg/day), with additional vitamin E, to achieve a daily dosage of 200 mg/day. Specific syndromes may also be addressed by nutritional interventions (for example, cranberry juice consumption to reduce urinary tract infections) and may reduce antibiotic use in older adults, particularly those living in long-term care facilities. Drug-nutrient interactions are common in elderly individuals, and care providers should be aware of these interactions. Future research should evaluate important clinical end points rather than merely surrogate markers of immunity.

In 1900, only 1 of every 11 Americans was aged ≥65 years. As we enter the new millennium, this ratio has increased to 1 in 7 persons, and by 2050, conservative estimates suggest there will be 80 million Americans aged ≥65 years. In comparison with the general population, older Americans are twice as likely to visit the doctor and 3 times more likely to be hospitalized; their average hospital stays are twice as long, and they consume twice the number of prescription drugs. Thus, low-cost strategies to avoid disease and disability in this age group are imperative for the 21st century.

Infection is among the most common of disorders in older Americans, and elderly individuals are 2–10-fold more likely to die of a variety of infections than are young adults [1]. Immune senescence, the decline of immune responses caused by aging itself, rather than accompanying comorbid conditions, probably contributes to this risk. In this series on Aging and Infectious Diseases in *Clinical Infectious Diseases*, Castle [2]

recently provided an excellent review of immune senescence and its clinical impact. Although growth hormone, thymic hormones, and cytokine strategies have achieved limited success in reversing the immune dysfunction of advanced age, nutritional interventions have proven to be effective (and inexpensive) strategies to ameliorate immune senescence. This review will examine the clinical data supporting specific nutritional approaches to reverse immune senescence, boost vaccine responses, and prevent infection in older adults.

EPIDEMIOLOGY OF MALNUTRITION IN ELDERLY PERSONS AND CLINICAL RELEVANCE

Although malnutrition is rare in the United States and other developed countries, elderly persons represent a population at significant risk (table 1) [3–7]. Physical conditions common in elderly persons, which include disability, medication-induced anorexia, poor dentition, restrictive diets, gastrointestinal diseases, and metabolic disorders (such as diabetes mellitus and renal failure), all affect nutritional intake and metabolic demand. Furthermore, cultural and psychosocial issues, such as living alone, bereavement, situational depression, and religious beliefs, may reduce nutrient intake and affect an elderly person's use of social services, such as Meals on Wheels. Finally, system barriers may exist that reduce dietary intake, particularly in

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persons who live in long-term care facilities (LTCFs) where restrictive meal times may limit the capacity to “graze” and where inadequate staffing may not allow sufficient devotion of personnel time to assist those who cannot feed themselves.

Global malnutrition (reduced intake or increased requirements for protein and calories) is the most common nutritional deficit in the elderly population. Up to 65% of older adults admitted to the hospital are undernourished, and malnutrition in hospitalized elderly patients is associated with significant adverse clinical outcomes [5, 8–15]. Studies suggest that both institutionalized and community-dwelling elderly individuals are at risk, with depression, medications, oral disorders (e.g., ill-fitting dentures), dementia, and concomitant illness (e.g., poorly controlled diabetes) leading the list of reversible causes [5, 16–18].

Micronutrient (vitamins and trace minerals) deficiencies are also common in older adults (table 1). Reduced oral intake, increased metabolic demands, and comorbidities, such as atrophic gastritis, all contribute to the increased risk of micronutrient deficiencies in elderly individuals. For example, zinc intake decreases throughout adult life and falls below the United States recommended dietary allowance of 0.2 mg/kg (12–15 mg/day) in the majority of older adults. Although levels of zinc in serum may be normal in older adults, cellular levels are often reduced [19].

DIAGNOSIS OF MALNUTRITION IN ELDERLY INDIVIDUALS

Clinical clues of malnutrition in older adults include the following: low body weight, muscle wasting, sparse or thinning hair, dermatitis, cheilosis or angular stomatitis, poor wound healing, and peripheral edema (table 1). Useful office assessments of nutritional status have been validated in elderly adults [20, 21]. One helpful screen is simply to assess weight and height and calculate the body-mass index (BMI; weight in kg/[height in m]²). Barrocas et al. [21] suggest that older adults who experience >5% loss of body weight in 1 month, a body weight >20% below ideal body weight, or a BMI of >27 or <22 should undergo a thorough assessment of nutritional status.

Many methods used to identify malnourished elderly persons are not available in most LTCFs. However, there are a number of indicators, readily available from common data sets, which correlate with sophisticated measures of nutritional status. Blaum et al. [22] showed that the weight and BMI measures available in the Minimum Data Set closely correlate with more complicated measures of nutritional status, and the utility of BMI has been confirmed in another LTCF study [23]. Several studies have documented that a recent loss of >5% of body weight, a weight <90% ideal body weight for age and sex, and

complaints of anorexia by LTCF residents correlate with malnutrition [8, 9, 24].

ROLE OF MALNUTRITION IN AGE-RELATED IMMUNE DYSFUNCTION

As mentioned above, this journal recently published an excellent review of immune dysfunction in the elderly population with primary references [2]. Thus, only the major changes will be outlined here briefly to provide background.

Little age-related change has typically been identified in the innate immune response (e.g., complement activation, phagocytosis, intracellular killing), except as modified by comorbid conditions. Recently, however, it has become clear that there are significant changes in the more advanced functions of phagocytic cells that also act as antigen presenters (i.e., macrophages, dendritic cells, and related cell types), particularly with regard to cell-cell interactions. Although results vary from study to study, most available data suggest macrophages from older adults constitutively produce greater amounts of some cytokines (e.g., prostaglandin E₂, IL-6, IL-10), creating a cytokine milieu consistent with chronic low-grade inflammation. In contrast, cytokine production after activation by specific stimuli is reduced (e.g., IL-1). Furthermore, macrophages in elderly individuals are not equivalent to those of young adults for stimulating adaptive immune responses, and in some experiments, they inhibit the adaptive immune response of young adult lymphocytes [25, 26].

There are also marked changes in adaptive immunity with age, some of which may be a consequence of the changes in innate immunity. Age-adaptive immunity is characterized by a decrease in thymic hormones and increases in memory T cells with a reciprocal reduction in naïve T cells. With regard to cytokine production, there is some evidence of constitutive activation with excessive baseline production of the Th1 cytokine IFN- γ , but with a shift toward Th2 responses (increased IL-10) after activation by mitogen or antigen. Furthermore, there is decreased expression of T cell costimulatory molecules (CD28) and impaired T cell signal transduction, which probably contributes to the well-documented reductions of IL-2 and IL-2 receptor expression and impaired T cell proliferative responses seen with advanced age (reviewed in [2, 27, 28]). Thus, the aged immune phenotype can be summarized as one of constitutive activation with reciprocal blunting of stimulus-induced responses in both the innate and adaptive immune systems.

Whether malnutrition of elderly persons causes some or all of the immune dysfunction seen with aging has been debated for decades. Some authors have suggested that nutritional factors play a major role [4, 29–32], whereas others have suggested that nutrition plays a minor role [33]. As with most scientific disagreements, the truth probably lies somewhere in the middle.

Table 1. Nutritional deficiencies that are common in elderly individuals.

Nutrient	Estimated prevalence, % ^a		Physical signs and symptoms and laboratory evidence of deficiency
	Long-term care facility or hospital	Community	
Global ^b	17–85	10–25	Weight loss, anorexia, depression, muscle wasting, low body-mass index, dermatitis, depression, peripheral edema, low serum albumin, lymphopenia
Vitamin A	2–20	2–8	Usually asymptomatic; skin dryness, corneal changes, night blindness
Vitamin B ₁₂	—	7–15	Usually asymptomatic; dementia, depression, neuropathy, megaloblastic anemia
Vitamin D	20–40	2–10	Often asymptomatic; weakness, osteoporosis/osteomalacia
Vitamin E	5–15	—	Usually asymptomatic; cerebellar ataxia, decreased reflexes, myopathy
Zinc	—	15–25	Often asymptomatic; loss of taste, lethargy, poor wound healing

^a True prevalence is dependent on the measure employed (i.e., intake, serum levels, tissue levels, change in physiologic measures).

^b Protein/calorie malnutrition.

The debate about the role of nutrition in immune dysfunction of elderly individuals is fueled by the definition of “deficient.” Deficiency is often defined by reduced dietary intake, but it is not clear what the “recommended” daily amount of vitamins or minerals should be for older adults [34, 35]; for some micronutrients, such as vitamin E, the recommendation is well below the level needed to optimize immune function [36, 37].

Although it is not clear whether nutritional factors *cause* immune senescence, animal and human studies support dietary strategies as a means to reverse the aged immune phenotype. Thus, efforts to identify specific nutritional deficiencies in the elderly population, by means of the strategies outlined above, appear to be warranted. Furthermore, a limited number of studies have employed pharmacologic doses of nutritional supplements, have been powered to detect clinical end points in specific groups of older adults, and have demonstrated a reduction in the risk of infectious illness. These studies are outlined in the sections below.

NUTRITIONAL SUPPLEMENTATION TO ENHANCE IMMUNE RESPONSES AND PREVENT INFECTION

Despite evidence that malnutrition in elderly persons is associated with poor immune function and adverse outcomes, few studies have shown that nutritional support can improve clinical outcomes in this population. These studies are difficult to perform, are rarely performed in patients who are hospitalized or in nursing homes, and require large numbers of subjects to

detect significant clinical end points. Thus, most studies employ surrogate markers of immune response (e.g., antibody titers, delayed-type hypersensitivity [DTH] responses, lymphocyte functional assays) [19, 36, 38–63].

Multivitamin Supplements

Multivitamin or mineral supplements have been used in a variety of study designs. All these studies report enhancement of at least some surrogate markers (e.g., DTH responses, cytokine production). To our knowledge, there are only 2 interventional studies that have shown benefit for the prevention of clinical events in elderly patients, one of which involved outpatients [38] and the other of which involved LTCF residents [59]. The community study provided a custom supplement of retinol, β -carotene, thiamine, riboflavin, niacin, pyridoxine, folate, iron, zinc, copper, selenium, iodine, calcium, magnesium, and vitamins B₁₂, C, D, and E to healthy adults in the community. The design was a 12-month-long, double-blind, randomized, placebo-controlled trial, and all subjects received supplements regardless of baseline nutritional status. During the 1 year of the study, there was less overall vitamin deficiency, an increase in CD4⁺ T cell percentages, natural killer cell activity, mitogenic responses, and IL-2/IL-2 receptor expression in the group that received the supplement. Most importantly, infectious “illness days” were reduced from a mean of 48 in the placebo group to 23 in the group that received the supplement ($P = .002$), and antibiotic use was lowered from an average of 32 to 18 days ($P = .004$).

Specific micronutrient supplementation may be of value.

However, the lack of clear benefit and potential harm in the use of some vitamins, such as vitamin A [47, 55, 64, 65], should discourage the use of high-dose supplementation at this time, except where clinical trials have shown benefit, as outlined below.

Trace Mineral Supplementation

The study of institutionalized elderly persons that demonstrated benefit by means of clinical end points [59] suggests trace minerals, rather than vitamins, may be the key nutritional factor for preventing infection in older adults. Zinc (20 mg of elemental Zn⁺⁺) plus selenium (100 µg) given daily, regardless of whether they were given with or without vitamins, decreased infection rates in that study [59] and barely missed significance in a similarly designed second, larger trial ($P = .06$) [60]. Both studies employed a factorial design (vitamins, trace minerals, both, or neither) in LTCF residents. The mean number of infections (respiratory and urinary tract) was reduced in both groups of subjects who took trace elements, as compared with those who took placebo or vitamins alone.

Other studies of zinc supplementation in older adults that have employed several forms and dosages of zinc have demonstrated enhanced DTH responses, and many have shown enhanced lymphocyte numbers and function of natural killer cells but no benefit for boosting humoral immune responses (table 2) [19, 41, 42, 47–51, 59–61].

Although most hypotheses have centered on trace elements boosting host immune response as the beneficial mechanism, recent data on viral virulence raise a fascinating alternative hypothesis. Data in selenium-deficient mice infected with either Coxsackie [66] or influenza virus [67] demonstrate that viral replication within nutritionally deficient hosts can lead to mu-

tations in the virus that alter its virulence, increasing the severity of illness even in well-nourished hosts. Thus, nutritionally deficient hosts may contribute to mutations in the viral genome during replication within the host and produce viruses with enhanced virulence [67]. This important host-organism interaction has not been confirmed in humans, but it could account for the severity of viral disease outbreaks in the nursing home setting or similar facilities, such as senior day care centers, and it deserves further study.

Vitamin E

Vitamin E, an antioxidant vitamin that has been extensively investigated as a preventive measure for many human conditions, including heart disease and cancer, also boosts immune responses in elderly recipients [36, 40, 52, 53, 68, 69] (table 3). It is not clear how vitamin E augments immune responses; it may do so by altering cytokine generation from T cells or macrophages [25, 70–73]. Although data regarding doses of vitamin E <200 mg/day are inconsistent [68, 69, 40], daily supplementation of 200 mg/day or 800 mg/day of vitamin E in healthy older adults improves DTH responses and augments primary immunization responses to hepatitis B (a T cell–dependent antigen) [36, 52, 53]. In those studies, there did not appear to be any greater benefit of a dosage of 800 mg/day when compared with 200 mg/day [36, 74]. There is also not any clear benefit of vitamin E administration with regard to vaccine responses to recall antigens (diphtheria and tetanus) or T cell–independent antigens (pneumococcal polysaccharides). No vitamin E supplementation studies that have involved elderly subjects have been powered to detect clinical end points, such as reduced illness days or antibiotic use; however,

Table 2. Recent trace mineral (i.e., zinc [Zn], selenium) supplementation trials in older adults.

No. of subjects in sample	Duration of study	Trial type	Nutrients	Major findings	Reference
81	2 years	R, P, F	Zn ⁺⁺ plus selenium <i>or</i> vitamins A, C, E; both or neither	Increased serum selenium levels in Zn ⁺⁺ plus selenium group and both group; decreased infectious episodes in the groups that received Zn ⁺⁺ and selenium, but not the group that received vitamins alone	[59]
118	3 months	R, P, F	Vitamin A, Zn ⁺⁺ , both or neither	Decreased CD3 ⁺ cells and CD4 ⁺ in vitamin A group, increased CD3 ⁺ , CD4 ⁺ , CD16 ⁺ and CD56 ⁺ lymphocytes	[47]
384	2 months	R	Zn ⁺⁺ or Zn ⁺⁺ plus arginine	No difference in percentage of responders or mean antibody titer after influenza vaccination	[61]
725	2 years	R, P, F	Zn ⁺⁺ plus selenium <i>or</i> vitamins A, C, E; both or neither	Increased serum micronutrient levels, but no effect on delayed-type hypersensitivity responses; improved responses to influenza vaccine in Zn ⁺⁺ plus selenium groups, borderline reduction in respiratory infection in Zn ⁺⁺ plus selenium groups ($P = .06$), no effect of vitamins alone	[60]

NOTE. F, factorial; P, placebo controlled; R, randomized.

Table 3. Randomized, placebo-controlled trials of vitamin E supplementation in older adults.

No. of subjects in sample	Duration of study, months	Vitamin E dosage	Major findings	Reference
161	6	50 or 100 mg/day	Borderline increased DTH, IL-2, and IL-4; decreased IFN- γ	[68]
88	8	60, 200, or 800 mg/day	Increased DTH and primary Ab responses (for T cell-dependent antigens) at ≥ 200 mg/day; borderline decrease in self-reported illness ($P = .10$).	[36]
52	3	100 mg/day	Little effect on mitogen T cell responses or Ig production	[69]
80	1–4.5	60, 200, or 800 mg/day	Increased DTH responses at all doses	[53]
32	1	800 mg/day	Increased DTH and IL-2 responses; decreased PGE ₂	[52]

NOTE. DTH, delayed-type hypersensitivity; PGE₂, prostaglandin E₂.

in one large study, the authors state that self-reported infections were 30% lower in vitamin E-treated subjects than they were in subjects who received placebo ($P = .10$) [36].

Nutritional Prevention of Specific Infectious Syndromes in Older Adults

Pressure ulcers. A recent multicenter trial [75] demonstrated a slightly reduced risk of pressure ulcers in LTCF residents who used protein/calorie supplements. However, there continues to be debate regarding the effectiveness of this intervention [76–78]. More widely accepted, but no more supported by well-controlled data, is the use of zinc supplements. Most of the data suggest that, if there is a benefit of zinc supplements for the prevention of pressure ulcers, it is confined to those patients who are zinc deficient at baseline. Thus, current recommendations [76] are to provide adequate protein and calories, and zinc sulfate at a dosage of ~ 220 mg/day to promote healing of pressure ulcers in patients with active wounds (note that higher dosages of zinc may increase adverse effects without additional benefit [79]), but nutritional supplements should not be provided solely for the prevention of pressure ulcers.

Urinary tract infections. Nutritional intervention for the prevention of urinary tract infection (UTI) in elderly subjects may be useful and inexpensive. Consumption of cranberry juice to prevent UTI (reviewed in [80]) has been studied in LTCF residents [81] and aging adults. Symptomatic UTI was reduced ($P = .01$), but only in young adult outpatients [82]. There are valid criticisms against these studies, such as the fact that the large, randomized trial that involved young adults [82] reduced bacteriuria with pyuria (15% in the 300 mL/day cranberry juice group vs. 28% in the control group), not symptomatic UTI. However, there are specific issues in the elderly population that may make drinking cranberry juice valuable. For example, the same randomized study of cranberry juice [82] showed a trend toward reduced antibiotic use in the treatment group (1.7 vs. 3.2 antibiotics per 100 patient months); if confirmed in a larger study of the elderly population, this would be of great value in and of itself. Furthermore, many studies have shown that

asymptomatic bacteriuria in elderly persons does not require therapy. However, the clinical dilemma is in the “mildly symptomatic” elderly adult (i.e., those with slightly reduced activities of daily living or oral intake, or low-grade temperature elevations). Such elderly people often get treated in attempts to clear the “symptoms.” One possible mechanism for reducing antibiotic use in older adults could be a reduction in malodorous urine, a common trigger for urinalysis and urine culture for institutionalized elderly persons [80].

NUTRITIONAL THERAPY DURING INFECTION

Nutritional therapy, enteral or parental, has been used in a large number of studies for many serious illnesses, but few have specifically focused on elderly subjects with infectious diseases. Several investigators have examined vitamin C (ascorbic acid) as adjunctive therapy for respiratory tract infections. One such study was performed in hospitalized elderly patients with bronchitis or pneumonia [83]; it compared vitamin C 200 mg/day with placebo in 57 patients. Supplementation rapidly increased plasma and cellular vitamin C levels and may have slightly improved functional status, particularly in those subjects with severe illness at admission. However, variable durations of follow-up, small numbers of patients, and unplanned subgroup analyses suggest that these data must be interpreted with caution.

Zinc supplementation has been suggested for elderly subjects to promote wound healing, particularly for venous stasis ulcers. A meta-analysis [84] suggests that zinc supplementation is of minimal value, if any. The appropriate dosage and duration are not known, but most studies used 200–220 mg of zinc sulfate t.i.d., and daily doses of >440 mg zinc sulfate (~ 100 mg of elemental zinc) may be detrimental [79].

NUTRITIONAL THERAPY AFTER INFECTION

Perhaps the most poorly studied aspect of nutritional therapy is its use after a serious infectious illness. Such patients have proven their risk of serious infection and are often malnour-

ished, as outlined in the sections above. A study from Spain [85] suggests that up to 85% of elderly patients with community-acquired pneumonia are malnourished. Data from surgical patients suggest that elderly individuals remain at risk for malnutrition during convalescence, with weight loss continuing for up to 8 weeks after hospital discharge. In an effort to address these issues, Woo et al. [86] studied the effect of nutritional supplementation during convalescence from community-acquired pneumonia in a group elderly patients, most of whom lived in the community. Patients were randomized to receive 500-mL of a commercially available supplement (Ensure; Abbott Laboratories) per day or nothing for 1 month after discharge. Several nutritional variables improved in the supplemented group, and elderly subjects who received supplements were more likely to achieve a higher functional status during follow-up visits (up to 3 months). Unfortunately, the study was not powered to detect differences in survival or recurrent infection and did not perform any measurements of immune function.

APPETITE STIMULANTS

Appetite stimulants have been modestly studied in older adults, but only for weight gain and other surrogate markers; no study has shown benefit with regard to prevention of infection or illness. The Council for Nutritional Clinical Strategies in Long-term Care recently reviewed this topic in the elderly population and concluded that, of the appetite stimulants studied, the evidence in support of the use of megestrol acetate (MA) is strongest in the current literature [87]. This conclusion is supported by a randomized, double-blind trial that involved LTCF residents [88] in which 800 mg/day of MA or placebo was provided for 12 weeks to residents with weight loss or low body weight. Study participants were followed-up for an additional 13 weeks for subsequent health outcomes, and the MA recipients were more likely to have gained weight than were the placebo recipients; however, again, the study was not powered to determine other important clinical end points.

The mechanism of MA activity is not clear, but there are some data to suggest MA inhibits catabolic enzymes (e.g., lipoprotein lipase) [89, 90] or may act via suppression of cytokines (IL-6, TNF- α , IFN- γ) [91, 92]. In addition, a cautionary note regarding the use of MA should also be sounded. MA is a steroid with glucocorticoid-like activity in addition to its androgenic properties [93]. Use of MA in other patient groups has been associated with the induction of Cushing's syndrome, diabetes mellitus, and suppression of the adreno-pituitary axis, which may lead to adrenal insufficiency with MA withdrawal [93–95].

DRUG-NUTRIENT INTERACTIONS

Older adults are likely to be receiving multiple prescription drugs. Increasingly, there is recognition that nutrient-drug interactions can cause serious adverse effects [87, 96]. In a recent study of residents in LTCFs [97], residents consumed a mean of 5 drugs per patient and were at risk for 1.4–2.7 drug-nutrient interactions per month. With specific regard to infection and antibiotic administration, tetracyclines and fluoroquinolones may be poorly absorbed when antacids, divalent cations (i.e., calcium), or tube feedings are provided. Certain antifungal compounds, particularly itraconazole, may be poorly absorbed with concomitant antacids or H₂ antagonists or proton pump inhibitor use. A critical part of nutritional care for older adults is frequent, thorough review of all medications with discontinuation of nonessential therapies.

CONCLUSIONS AND RECOMMENDATIONS

The elderly population is at special risk for malnutrition that may lead to an increased risk of infection. Reversible causes of malnutrition, such as depression, dental disorders, and medication-induced anorexia, are common in elderly individuals, and they are underrecognized and undertreated. Given the diversity of data and the lack of appropriately powered studies to detect clinical end points, specific recommendations are problematic at this time. However, the majority of data suggest that a multivitamin or trace mineral supplement taken daily is beneficial for the prevention of infection and may reduce antibiotic use in healthy, free-living elderly adults. The supplement provided should include zinc (20 mg/day of elemental zinc or its equivalent) and selenium (100 μ g/day), with additional vitamin E, to achieve a daily dosage of 200 mg/day. Specific micronutrient (e.g., vitamin B₁₂)–replacement therapy makes sense and should be provided for patients with documented deficiencies, but data regarding protective efficacy specifically addressing infection are lacking. Some selected elderly adults may benefit from nutritional strategies (e.g., elderly adults with frequently recurring UTIs are likely to benefit from drinking cranberry juice every day). This strategy may be particularly beneficial in LTCFs as a means of reducing unnecessary antibiotic use in older adults. Commercially available nutritional supplements may be of benefit in older adults convalescing from serious infectious illnesses; specific data exist for daily consumption of a calorically dense supplement (i.e., Ensure) in older adults recovering from pneumonia.

Future studies should focus not just on healthy older adults, but on identifying specific groups of elderly persons (e.g., those with chronic obstructive pulmonary disease, extreme frailty) that may benefit most. Furthermore, in some elderly individuals with severe comorbidities, it is likely that nutritional supplementation is no longer able to overcome underlying immune compromises.

Thus, the limitations of nutritional supplements should be explored. Future clinical trials should be powered to adequately evaluate important clinical end points. Beyond mortality, vaccine responses and other surrogate markers of immune response, subsequent investigations should include infectious episodes (particularly those that are microbiologically documentable, such as *Clostridium difficile* colitis), antibiotic use, and antibiotic resistance, particularly in patients living in LTCFs.

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