Annals of Epidemiology 26 (2016) 342–347

Contents lists available at ScienceDirect

Annals of Epidemiology

journal homepage: www.annalsofepidemiology.org

The Microbiome and Epidemiology

The human microbiota: novel targets for hospital-acquired infections and antibiotic resistance

Melinda M. Pettigrew PhD [a,*], J. Kristie Johnson PhD, D(ABMM) [b], Anthony D. Harris MD MPH [c]

[a] Department of Epidemiology of Microbial Diseases, Yale School of Public Health, New Haven, CT
[b] Department of Pathology, University of Maryland School of Medicine, Baltimore, MD
[c] Department of Epidemiology, University of Maryland School of Medicine, Baltimore, MD

ARTICLE INFO

Article history:
Received 30 November 2015
Accepted 26 February 2016
Available online 8 March 2016

Keywords:
Microbiota
Hospital-acquired infection
Antibiotic resistance
Infection control
Antimicrobial stewardship
Clostridium difficile
Vancomycin resistant enterococcus

ABSTRACT

Purpose: Hospital-acquired infections are increasing in frequency due to multidrug resistant organisms (MDROs), and the spread of MDROs has eroded our ability to treat infections. Health care professionals cannot rely solely on traditional infection control measures and antimicrobial stewardship to prevent MDRO transmission. We review research on the microbiota as a target for infection control interventions.
Methods: We performed a literature review of key research findings related to the microbiota as a target for infection control interventions. These data are summarized and used to outline challenges, opportunities, and unanswered questions in the field.
Results: The healthy microbiota provides protective functions including colonization resistance, which refers to the microbiota's ability to prevent colonization and/or expansion of pathogens. Antibiotic use and other exposures in hospitalized patients are associated with disruptions of the microbiota that may reduce colonization resistance and select for antibiotic resistance. Novel methods to exploit protective mechanisms provided by an intact microbiota may provide the key to preventing the spread of MDROs in the health care setting.
Conclusions: Research on the microbiota as a target for infection control has been limited. Epidemiologic studies will facilitate progress toward the goal of manipulating the microbiota for control of MDROs in the health care setting.

Introduction

Hospital-acquired infections (HAIs) cause approximately 100,000 deaths per year in the United States and the five most common HAIs cost the US health care system $9.8 billion annually [1,2].

Approximately 20% of HAIs are due to multidrug resistant organisms (MDROs) [3]. Colonization of the gastrointestinal tract or other body sites by MDROs is often a first step in the establishment of infection [4]; of patients colonized with MDROs in the intensive care unit (ICU), approximately 20% will develop clinical infection with the same MDRO during their ICU stay [5–7]. Importantly, colonized patients also serve as a reservoir for transmission to others. MDRO's colonize the gastrointestinal tract, respiratory tract, and skin within the context of the microbiota, which is the community of microorganisms that inhabits our bodies. In healthy individuals, the microbiota provides protective functions including prevention of colonization by pathogens and/or expansion of low-density pathogens, (i.e., colonization resistance). Antibiotics and other hospital-associated exposures (e.g., dietary changes) alter the composition, diversity, and density of the microbiota and select for antibiotic resistance [8–10]. Hospitalization-related disruptions of the microbiota may reduce colonization resistance and increase risk for acquisition and expansion of MDRO. Thus, the microbiota may provide a critical target for prevention strategies to limit colonization and spread of MDROs in the health care setting.

Research on the potential of the microbiota as a target for infection control has been limited to mechanistic studies in murine models and clinical studies with small numbers of patients and/or highly restricted patient populations. Epidemiologic studies will inform the development of novel interventions to exploit the protective mechanisms provided by an intact microbiota. The goals of this review are to describe limitations of traditional infection control interventions, to summarize key research findings related to the microbiota as a target for infection control interventions, and to

* Corresponding author. Department of Epidemiology of Microbial Diseases, Yale School of Public Health, 60 College Street, LEPH 720, New Haven, CT 06515. Tel.: +1-203-737-7667; fax: +1-203-785-4782.
E-mail address: melinda.pettigrew@yale.edu (M.M. Pettigrew).

http://dx.doi.org/10.1016/j.annepidem.2016.02.007
1047-2797/

outline challenges, opportunities, and unanswered questions in the field.

Limitations of traditional measures to prevent HAIs with MDROs

Traditional infection control measures include barrier precautions, hand hygiene, decolonization of patients, and environmental decontamination [11] and can reduce the incidence of HAI [12–14]. However, various infection control interventions have produced inconsistent results, and it is clear that infection control measures alone cannot prevent the spread of MDRO because MDRO rates continue to increase [13,15,16]. Antimicrobial stewardship programs are also critical for achieving reductions in the prevalence and spread of MDROs. The successes that are achieved by antimicrobial stewardship programs may be difficult to sustain because increases in the prevalence of MDRO's often lead to increases in empiric prescribing of broad-spectrum antibiotics, which then leads to a cycle of increased antibiotic use and increased resistance [17,18]. Controlling the spread of MDROs in the health care setting will require novel and multifaceted approaches above and beyond the current infection control and antimicrobial stewardship interventions.

Role of the microbiota in preventing acquisition and/or expansion of potential HAI-associated pathogens

In healthy individuals, the gastrointestinal microbiota provides several important immunologic, metabolic, and protective functions including colonization resistance [19,20]. Colonization resistance was first described in a series of seminal articles dating back to the 1970s [21,22]. These studies examined the impact of antibiotics on the gastrointestinal flora and showed that (1) a lower infectious dose of pathogens (e.g., *Escherichia coli*, *Pseudomonas aeruginosa*) was needed to establish colonization in mice who had received antibiotics, (2) antibiotic treatment resulted in overgrowth and/or expansion of exogenous pathogens, and (3) the extent of colonization resistance differed by the antibiotic used [21,22]. Colonization resistance was attributed to anaerobic bacteria that were abolished by antimicrobial treatment [21]. Colonization resistance may be preserved in the presence of some antibiotics, for example, β-lactamase producing anaerobes help preserve colonization resistance in the gut by inactivating β-lactam antibiotics [23,24]. Murine studies also indicate that in addition to colonization resistance, an intact microbiota can mediate clearance of gastrointestinal pathogens once infection has been established [25].

Mechanisms that mediate colonization resistance include competition for nutrients and adherence sites, direct inhibition of pathogens via substances excreted by members of the microbiota, and innate and adaptive immune responses induced by commensals [26,27]. Antibiotic induced changes in the composition and diversity of the gastrointestinal microbiome may also lead to the disruption of carbohydrate and bile metabolism and the loss of anaerobes that produce short-chain fatty acids [28,29]. Short-chain fatty acids help regulate regulatory T cells and promote homeostasis within the gastrointestinal tract and may play a critical role in colonization resistance [30], although some studies were unable to correlate short-chain fatty acid production with lower levels of pathogen colonization [31,32].

Impact of antibiotics on the microbiota

Antibiotics have a profound impact on the gastrointestinal and upper respiratory tract microbiota. Specific antibiotics favor survival of nonpathogenic and pathogenic species within the microbiota if they are resistant to the prescribed antibiotic. Antibiotics can alter bacterial loads, relative abundance of commensals, and lead to lower levels of diversity in the microbiota [8,9,33]. Dethlefsen et al. [33] studied three healthy volunteers receiving two courses of ciprofloxacin separated by 6 months and followed them for over 10 months. They observed a rapid loss of diversity within 3–4 days of ciprofloxacin exposure. Rebounds in bacterial diversity were observed after approximately 1 week, but the microbiota did not return to its original composition. Other authors have shown that the impact of antibiotics can persist for years after the original treatment [9].

Antibiotics exert a powerful selective pressure on the microbiota that extends beyond altering the prevalence of specific taxa. The microbiota provides a reservoir of resistance genes, termed the antibiotic resistome, which can be horizontally transferred within and across species and lead to the emergence of antibiotic resistance in pathogens [34,35]. Sommer et al. [36] characterized the reservoir of antibiotic resistance genes in the oral and gut microbiota in two healthy individuals who had no previous antibiotic exposure in the prior year. Of concern, close to half of the resistance genes from 572 cultured gastrointestinal bacteria strains were identical at the nucleotide level to antibiotic resistance genes previously identified in human pathogens. Hu et al. [37] examined the gut microbiota of 162 individuals from Spain, China, and the Netherlands and identified a total of 1093 antibiotic resistance genes. The high level of diverse antibiotic resistance determinants represents a substantial reservoir of genes that could potentially be transferred to, and emerge in, human pathogens. The antibiotic resistome also contains cryptic resistance genes that may evolve into resistance genes under appropriate conditions [34]. Some genes within the antibiotic resistome may have sequence matches to known resistance genes but may not be functional [38]. Moreover, there may be barriers to gene exchange with human pathogens in the case of certain resistance genes. Epidemiologic studies, including randomized controlled trials, can address questions regarding the differential impact of different classes of antibiotics on the antibiotic resistome and track how resistance determinants spread in the health care setting.

Factors affecting the microbiota and risk of colonization and disease in hospitalized patients

To this point, studies of the impact of antibiotics on the microbiota have most often focused on healthy individuals [9,33]. Exposures are quite different in hospitalized patients. In addition to receiving multiple courses of antibiotics, hospitalized patients are exposed to other factors such as stress, intravenous nutrition, and other medications, which all may impact the microbiota. Zaborin et al. [39] examined fecal samples from 14 ICU patients and five healthy controls. The flora of healthy volunteers contained approximately 40 genera and high relative abundances of Firmicutes and Bacteroidetes. In contrast, 36% of the ICU patients had extremely low levels of diversity, defined as having >90% abundance of one bacterial taxon. These patients also experienced rapid fluctuations in the flora and replacement of one dominant taxon by another. The microbiota of hospitalized patients was dominated by *Enterococcus*, *Staphylococcus*, and Enterobacteriaceae, phylogenetic groups that include potential HAI-associated pathogens and MDROs [39]. These data provide important insights into the potential differences in the microbiota between healthy individuals and hospitalized patients. However, the study contained a small number of subjects presenting with a diverse range of medical conditions and length of hospital stay. Individuals respond differently to antibiotic treatment [9,33]. Factors such as age, presence of comorbid conditions, types of medical interventions, and length of stay can also impact the risk of MDRO acquisition [3,40–43]. Thus, it