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Genomic transition of enterococci from gut commensals to leading causes of multidrug-resistant hospital infection in the antibiotic era

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The enterococci evolved over eons as highly adapted members of gastrointestinal consortia of a wide variety of hosts, but for reasons that are not entirely clear, emerged in the 1970s as leading causes of multidrug resistant hospital infection. Hospital-adapted pathogenic isolates are characterized by the presence of multiple mobile elements conferring antibiotic resistance, as well as pathogenicity islands, capsule loci and other variable traits. Enterococci may have been primed to emerge among the vanguard of antibiotic resistant strains because of their occurrence in the GI tracts of insects and simple organisms living and feeding on organic matter that is colonized by antibiotic resistant, antibiotic producing microorganisms. In response to the opportunity to inhabit a new niche — the antibiotic treated hospital patient — the enterococcal genome is evolving in a pattern characteristic of other bacteria that have emerged as pathogens because of opportunities stemming from anthropogenic change.

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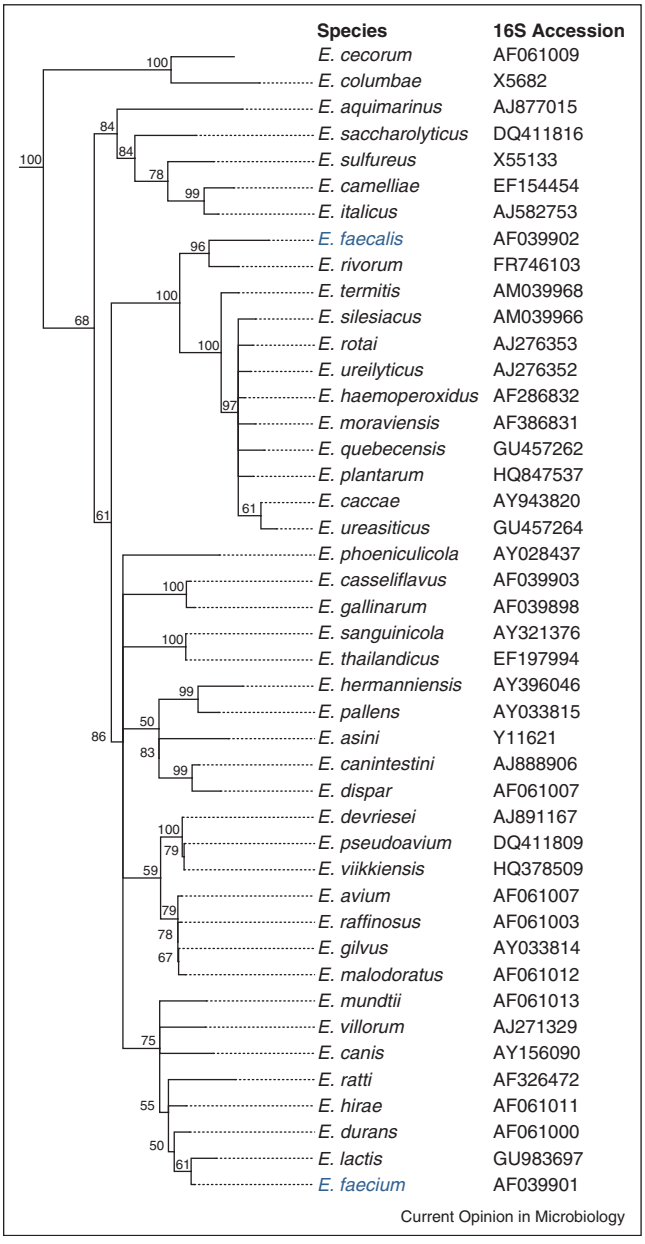
Introduction

Enterococci began to emerge as leading causes of multidrug resistant hospital acquired infection in the 1970s and 1980s [1•,2]. They now rank among leading causes of hospital acquired infection of the bloodstream, urinary tract, surgical wounds and other sites [3]. Before that, enterococci isolated from infections were generally regarded as contaminants [1•]. Two species of *Enterococcus* are mainly responsible for hospital infections — *Enterococcus faecalis* and *Enterococcus faecium* (Figure 1). The most recent data available on enterococcal infection from all infection sites and all classes of hospitals in the US, which covers the period 01/01/10–06/30/12, identified 9309 bloodstream isolates, 54,709 urinary tract isolates, and 20,032 wound isolates (84,050 isolates total) (TSN® Database, Eurofins, Inc., personal communication Daniel F. Sahm, Ph.D.). Of the total, 17,360 are vancomycin resistant (20.6%), and 64,015 (76%) are *E. faecalis*. Although 24% of isolates are *E. faecium*, they represent 14,998 of the 20,038 (75%) of the vancomycin resistant isolates. Similar trends have been reported for the European Union [4,5]. *E. faecium* infection appears to be highly dependent on resistance to last line drugs, whereas *E. faecalis* has a greater innate capacity to cause infection irrespective of resistance [2,6]. Interestingly, even though *E. faecium* are more dependent on vancomycin resistance to cause infection, and are more likely to be vancomycin resistant, *E. faecalis* is the primary species that has transmitted vancomycin resistance to *Staphylococcus aureus* [7].

Despite emergence as leading causes of antibiotic resistant infection, enterococci evolved over eons to be members of a broad range of GI tract consortia. In the 1960s and 1970s Mundt *et al.* [8••,9] grew enterococci from the GI tracts of mammals (71.3%), reptiles (85.7%), birds (31.8%) and insects (53%) (culture-positive rates typically underestimate carriage several fold [10], meaning that the actual rate of colonization may be closer to 100%). This indicates that since at least the early Devonian period ~412 MYA [11] (time of last common ancestor of mammals, reptiles, birds and insects), enterococci have been ubiquitous members of gut microbiomes. Enterococci may in fact have been among the earliest members GI tract consortia. The phylogeny of the genus *Enterococcus* is shown in Figure 1.

Reflecting their highly evolved role as members of a consortium in an extremely competitive environment, enterococci have reduced genomes. *E. faecalis* (cited as *Streptococcus zymogenes* [12••]) has long been known to require a number of amino acids (including Val, Leu, Ile, Ser, Met, Glu, Arg, His and Trp) and vitamins (including biotin, nicotinic acid, pantothenate, pyridoxine, riboflavin, and sometimes folic acid) for maximal growth, with other species being similar in their fastidiousness. The

Figure 1



Dendrogram of the genus *Enterococcus*. A dendrogram of all available 16S rDNA sequences for members of the *Enterococcus* genus was compiled using the Geneious software (Biomatters Ltd) using the neighbor-joining algorithm and the 16S sequence of *Tetragenococcus solitarius* as an outgroup. Boostrap values were generated over 1000 iterations. The species *E. faecalis* and *E. faecium* are highlighted in blue.

implication is that it is more efficient (i.e. there is a selective advantage) for enterococci to acquire these nutrients from their habitats (e.g. diet of the host or cross-feeding relationships with other microbes in the gut consortium), as opposed to carrying the additional genetic material necessary for their biosynthesis from simpler precursors. In other words, the intense competition in the complex milieu of the gastrointestinal tract has led to a well-adapted, streamlined enterococcal genome.

Commensalism for microbes is not simply the absence of virulence traits, but the active production of factors that lead to stable relationships and limit entry into potentially pathogenic pathways. The transition from commensal to pathogen appears to be associated with changes in ecologies that open new habitats or routes of transmission. Mechanisms that contribute to destabilization of the commensal/host relationship include the acquisition of toxins, or blocks of genes related to pathogenesis, such as pathogenicity islands [13•]. Alternatively, virulence can result from the loss of key commensal functionality, such as appears to have occurred in *Bordetella pertussis*. *B. pertussis* is 99.8% identical at the 16S rRNA level to the much less virulent species *Bordetella bronchoseptica*, but through deletion of 20% of the genome, and conversion of 10% more into pseudogenes by proliferation of the insertion element IS481, it has lost the ability to colonize the host in a nonpathogenic manner [14••,15•]. Similarly, *Yersinia pestis* evolved from less virulent *Yersinia pseudotuberculosis*, mainly by the inactivation of 15% of its genome by deletion and IS element proliferation and acquisition of a virulence plasmid. It is likely in both *B. pertussis* and *Y. pestis*, that rapid proliferation of IS elements led to the destabilization of the chromosome, contributing to numerous inversion and deletion events [14••,15•,16].

Evidence for the recent devolution of the commensal enterococcal genome, leading to a hospital adapted pathogen

We [17] and others [18–20] observed that most multidrug resistant hospital infections caused by enterococci were caused by hospital endemic, clonal lineages. For example, in a retrospective study of an outbreak of 206 enterococcal bacteremias over a 36-month period (1984–1987), we found that 190 were caused by *E. faecalis*, most of which were resistant to high levels of aminoglycosides and macrolides [17]. Moreover, nearly half of the 190 infections were caused by a single *E. faecalis* strain that was multidrug resistant as well as hemolytic, whereas the remainder were caused by largely nonhemolytic idiosyncratic strains with few identities to each other or the hospital endemic clone, based on pulsed field electrophoresis pattern [17]. The prototype strain, termed MMH594, had become highly hospital adapted and unusually pathogenic, capable of repeated bed-to-bed transmission. In parallel studies, colleagues at Barnes-Jewish Hospital at Washington University isolated the first vancomycin resistant *Enterococcus* in the US from the bloodstream, urine and feces of a chronically infected HIV/AIDS patient who had received vancomycin therapy [21•]. *E. faecalis* V583 manifests a novel vancomycin resistance phenotype, termed VanB, but otherwise possessed numerous similarities to MMH594 [21•].