As our understanding of the pathophysiological processes of sepsis evolves, it becomes clear that morbidity and mortality are attributed to the type of inflammatory response launched by the host, rather than to the specific microbial trigger itself. A crucial question that has troubled clinicians for some time is why specific infections may trigger severe sepsis and death in some patients, while in others infection may be battled successfully. Recent advances in unraveling genetic variations in processes such as the innate immune response, coagulation, cell signaling, and cellular response to stress suggest that the response to inflammatory triggers, and probably susceptibility to sepsis, may be highly individualized, partially due to subtle differences in genetic makeup, that is, the presence of polymorphisms. Polymorphisms are natural variations in a gene, or DNA sequence, so that at least 2 alleles (alternative forms of a DNA locus) are present and discussed. Study results are often discrepant, whereas many methodological limitations, in terms of both study design and genotyping methods, may render the results difficult to generalize. Nonetheless, a role for genomic variations in sepsis outcomes has emerged. A theoretical framework for incorporation of genetic variations into individualized care planning based on complexity theory is proposed, and future prospects of microarray technology and systems modelling are discussed briefly.

**Keywords:** coagulation, complex systems theory, cytokines, polymorphism, sepsis
present. In contrast to mutations, polymorphisms may be very common, involving 1% of the population or more. Polymorphisms may range from alterations of noncoding DNA sequences without any phenotypic effect, to any degree of variation with corresponding detectable phenotype alterations. Single nucleotide polymorphisms (SNPs) are allelic variations in a single base pair, due to either insertion, deletion, or substitution, and may occur in exons, introns, or promoter regions of a gene (Figure 1).

This article aims to critically review evidence on the role of genetic polymorphisms in the pathogenesis of sepsis, based on studies conducted primarily in human and secondarily in animal subjects. A literature review of the MEDLINE and PubMed databases was carried out (Table 1). The potential role of polymorphisms in essentially all the crucial pathogenetic events of sepsis will be highlighted. Implications for nursing research, practice, and theory will be discussed, as well as some future ramifications of genetics for the theory

**Figure 1:** A, Schematic representation of genomic variations that commonly occur in the DNA. B, Schematic representation of DNA loci where single nucleotide polymorphisms (SNPs) may occur. SNPs usually occur at the noncoding region and they do not affect gene expression. SNPs at the promoter region of the gene may affect gene expression, whereas SNPs at introns or exons may interfere with protein structure.
Table 1: Summary of Studies That Support an Association Between Specific Gene Polymorphisms and Susceptibility and/or Outcome of Sepsis and Related Syndromes in Humans

<table>
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<tr>
<th>Author(s), Year, Type of Study, Country of Origin</th>
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<tr>
<td><strong>TNFA Gene Polymorphisms</strong></td>
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</tr>
<tr>
<td>Mira et al, 1999, multicenter case-control, France</td>
<td>−308 G/A (89 patients with septic shock, 87 healthy unrelated controls)</td>
<td>The A allele (TNF2) was more frequent in patients with septic shock than in controls (39% vs 18%). Patients with TNF2 had a 3.7-fold risk of death (95% CI = 1.37–10.24).</td>
</tr>
<tr>
<td>Jaber et al, 2004, prospective correlational, USA</td>
<td>−308 G/A (and IL10 −1082 A/G) (61 acute renal failure patients with intermittent hemodialysis)</td>
<td>The A allele carrier state was associated with a higher risk of death (HR = 2.5). The TNFA high and IL10 low producer genotype was associated with an ~6-fold increased risk for death compared to the TNFA low and IL10 intermediate/high producer genotype.</td>
</tr>
<tr>
<td>Waterer et al, 2001, Prospective genetic association, Australia</td>
<td>−308 G/A (and TNFB 250 G/A) (31 septic shock and 80 respiratory failure patients)</td>
<td>Carrying at least 1 AA genotype had an 18.0% (vs 6.8%) risk of septic shock. GG homozygotes (TNF low secretors) at both loci had a 2.9% risk of septic shock. Septic shock was associated with the TNFB 250:TNFA−308 A:G haplotype but not the A:A haplotype, suggesting that TNFB 250 may not be causative. Carriage of the G:G haplotype had a protective effect against septic shock.</td>
</tr>
<tr>
<td>Appoloni et al, 2001, prospective genetic association, Belgium</td>
<td>−308 G/A (37 patients with recent septic shock)</td>
<td>TNF2 genotype was associated with increased risk for mortality (OR: 12; 95% CI: 1.4–96), and with TNFA levels.</td>
</tr>
<tr>
<td>O’Keefe et al, 2002, prospective genetic association, USA</td>
<td>−308 G/A (152 trauma patients)</td>
<td>A-allele carriage was associated with an adjusted OR of 4.6 (95% CI: 1.9–10.9) for severe sepsis and of 2.1 (95% CI: 0.6–7.3) for death.</td>
</tr>
<tr>
<td>Watanabe et al, 2005, 1 group genetic association, Japan</td>
<td>−238 G/A, −308 G/A (113 SIRS patients)</td>
<td>Associations were found between susceptibility to septic shock and poor prognosis and carriage of the TNFA−308 A allele.</td>
</tr>
<tr>
<td>Tomasdottir et al, 2003, 1 group genetic association, Sweden</td>
<td>−308 G/A (95 elective cardiac surgery patients)</td>
<td>Homozygotes for the polymorphism had a higher incidence of left ventricular dysfunction (OR: 3.84; 95% CI: 1.40–24.3), postoperative pulmonary dysfunction (OR: 5.21; 95% CI: 1.49–18.3), and a lower pulmonary oxygenation index.</td>
</tr>
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<tr>
<td>*Reid et al, 2002, prospective genetic association, UK</td>
<td>Polymorphisms in the $TNFA$, $TNFB$, $IL10$, and $TGFB1$ genes (88 MODS patients, 30 healthy controls)</td>
<td>High $TNFA$ producers were overrepresented (35.2% vs 16%) in the patient group. $TNFA$ genotype was not related to mortality. Patients predisposed to produce a balanced cytokine response (e.g., intermediate $IL10$/$TNFA$ producers) demonstrated the longest survival times. The $A$ allele was associated with increased 60-day mortality in ARDS. The association with susceptibility to ARDS depended on the site of the predisposing injury. The $A$ allele imparted increased risk for severe sepsis, relative to $GG$ homozygotes (OR: 4.5; 95% CI: 1.7–12). No association with mortality.</td>
</tr>
<tr>
<td>Gong et al, 2005, nested case-control, USA</td>
<td>$-308$ G/A (212 ARDS patients, 441 controls)</td>
<td>Patients with the heterozygous genotype had a 1.6-fold higher RR for complications. Patients homozygous for $TNFB2$ had a 1.5-fold higher RR for severe complications and higher mortality.</td>
</tr>
<tr>
<td>*Barber et al, 2004, group genetic association, USA</td>
<td>$-308$ G/A (and TLR4 896 A/G, CD14 –159, $IL1B$ –31, $IL6$ –174) (159 burn patients)</td>
<td>Homozygocity for the polymorphism associated with higher frequency of complications (81% vs 49%), and a lower capacity to produce $TNFA$ after the operation. Patients with severe sepsis were more likely to possess a homozygous polymorphic genotype. The $TNFB2$:TNF2 haplotype was negatively associated with development of severe sepsis.</td>
</tr>
<tr>
<td>Kahlke et al, 2004, prospective observational, Germany</td>
<td>NcoI polymorphism ($TNFB2$) (160 major gastrointestinal surgery patients)</td>
<td>Development of severe sepsis was significantly increased in patients homozygous for the polymorphism (OR = 5.22; 95% CI = 1.6–17.9). The distribution of $TNFB$ genotypes was different between controls and patients. The $TNFB2$:B2 genotype (high $TNFA$ levels) was less frequent in patients and was associated with higher mortality.</td>
</tr>
<tr>
<td>Riese et al, 2003, group genetic association, Germany</td>
<td>NcoI polymorphism (172 postoperative patients)</td>
<td></td>
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<tr>
<td>Majetschak et al, 2002, group genetic association, Netherlands</td>
<td>NcoI polymorphism (and $TNFA$ –308 G/A) (70 blunt trauma patients)</td>
<td></td>
</tr>
<tr>
<td>Majetschak et al, 1999, group genetic association, Germany</td>
<td>NcoI polymorphism (110 severe blunt trauma patients)</td>
<td></td>
</tr>
<tr>
<td>*Reid et al, 2002, prospective genetic association, UK</td>
<td>SNPs in $TNFA$, $TNFB$, $IL10$, and $TGFB1$ genes (88 MODS patients, 30 controls)</td>
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<tr>
<td>*Fang et al, 1999, prospective, consecutive entry, Germany</td>
<td>NcoI polymorphism (and IL1RN A2 (2 repeats), ILB TaqI) (93 severe sepsis patients)</td>
<td>TNFB2 was associated with nonsurvival</td>
</tr>
<tr>
<td>*Waterer et al, 2003, prospective genetic association, Australia</td>
<td>250 G/A (and HSP70-2 A/G) (93 severe sepsis patients)</td>
<td>250 AA genotype associated with septic shock (RR: 2.7). The greater risk of septic shock was associated with carriage of HSP70-2 A/T NFB 250 A haplotype.</td>
</tr>
</tbody>
</table>

**IL1B Gene Polymorphisms**

Read et al, 2003, genetic association, UK

*Val polymorphism at –511 (B2), 2018 polymorphism (1106 meningococcal disease patients, 839 controls) | Patients carrying the –511 common allele were more likely to survive (OR: 2.01; 95% CI: 1.11–3.79). |

*Ma et al, 2002, prospective consecutive entry genetic association, China

*Val polymorphism at –511 (B2) (a VNTR (86 bp, intron 2: RN2) of IL1RN gene, and a VNTR (46 bp: A2) of IL1A gene) (60 sepsis patients) | *Val polymorphism frequencies did not differ between septic patients and controls. Genotypes A2/2, B2/2, and RN2/2 were associated with higher mortality (70% to 80%). Patients with any 2 of the 3 alleles suffered from more severe sepsis and a higher mortality (65% to 85%), compared to patients with genotypes A1/1, B1/1, or RN1/1 (0% to 13%). |

**IL1A Gene Polymorphisms**

*Ma et al, 2002, prospective consecutive entry genetic association, China

*VNTR (46 bp, intron 6: A2) (a VNTR (86 bp) of IL1RN gene (RN2), and *Val polymorphism (~511) of IL1B gene (B2) (60 sepsis patients) | IL1A gene VNTR polymorphism frequencies did not differ between septic patients and controls. |

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Table 1: Summary of Studies That Support an Association Between Specific Gene Polymorphisms and Susceptibility and/or Outcome of Sepsis and Related Syndromes in Humans (Continued)

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<td><strong>IL6 Gene Polymorphisms</strong></td>
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<tr>
<td>Schüter et al, 2002, case-control genetic association, Germany</td>
<td>−174 G/C (326 surgical patients with an ICU stay ≥3 days, matched controls)</td>
<td>Genotype distribution and allele frequencies did not differ between patients with or without sepsis and controls. In septic patients, significantly less GG homozygotes were observed.</td>
</tr>
<tr>
<td>*Balding et al, 2003, case-control genetic association, Ireland</td>
<td>−174 G/C (and IL-10 −1082 G/A (183 meningococcal disease patients and 389 controls)</td>
<td>The G/G genotype was more frequent in nonsurvivors compared with survivors, and in patients with severe disease compared to those with mild disease.</td>
</tr>
<tr>
<td>Sutherland et al, 2005, group genetic association, Canada</td>
<td>Set of 3 SNPs (−174 G/C, 1753 C/G, 2954 G/C (228 critically ill patients with SIRS)</td>
<td>Patients with 2 copies of haplotypes −174C/1753C/2954G (C/C/G), G/G/G, or C/C/C had a greater 28-day mortality compared with patients with 1 or no copies of these haplotypes (40.0% vs 26.0%), and fewer days free of MODS. No associations between individual SNPs and survival or MODS.</td>
</tr>
<tr>
<td><strong>IL10 Gene Polymorphisms</strong></td>
<td></td>
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</tr>
<tr>
<td>Nakada et al, 2005, case-control genetic association, Japan</td>
<td>−592 C/A (197 critically ill patients, 214 healthy controls)</td>
<td>The −592 CC genotype was related to poor outcome in sepsis.</td>
</tr>
<tr>
<td>Wattanathum et al, 2005, genetic association, Canada</td>
<td>−592 C/A, +734 G/T, +3367 G/A (158 sepsis patients with pneumonia, 392 patients with extrapulmonary sepsis)</td>
<td>4 major haplotypes (CGG, AGG, CTA, CTG) identified. Pneumonia patients with 1 or 2 copies of the CGG haplotype had greater mortality (51.4% vs 29.1%). CGG carriers had more organ dysfunction. No association of genotypes with mortality or organ dysfunction in nonpneumonia patients.</td>
</tr>
<tr>
<td>*Balding et al, 2003, case-control genetic association, Ireland</td>
<td>−1082 G/A (and IL6 −174 G/C (183 meningococcal disease patients and 389 controls)</td>
<td>The <em>IL10</em> −1082 A/A genotype was more frequent in nonsurvivors compared with survivors, and in patients with severe disease compared to those with mild disease.</td>
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<tr>
<td>Stanilova et al, 2006, case-control genetic association, Bulgaria</td>
<td>$-1082$ A/G (33 severe sepsis patients, 53 healthy volunteers)</td>
<td>Carriage of the polymorphic allele resulted in a significant increase in $IL10$ production from stimulated PBMC. Surviving patients had lower $IL10 -1082$ G frequency, compared with controls (17% vs 47.2%).</td>
</tr>
<tr>
<td>Zhang et al, 2005, case-control genetic association, China</td>
<td>$-1082$ G/A (109 severe pancreatitis patients, 106 acute mild pancreatitis patients, and 116 controls)</td>
<td>Patients with septic shock showed a significantly higher prevalence of $-1082$ G allele than those without shock ($\chi^2 = 5.921$)</td>
</tr>
<tr>
<td>Shu et al, 2003, case-control genetic association, China</td>
<td>$-1082$ A/G (severe sepsis patients and healthy controls)</td>
<td>Patients with severe sepsis were more likely to have $IL10 -1082$ C allele, compared with controls. Genotype distribution differed between patients and controls. No association with survival.</td>
</tr>
<tr>
<td>Gallagher et al, 2003, group genetic association, Ireland</td>
<td>$-1082$ A/G (and $TNFA -308$ G/A and $IL6 -174$ G/C) (74 SIRS and 19 non-SIRS critically ill patients with pneumonia)</td>
<td>A significant stepwise increase in frequency of the $IL10 G$ allele, associated with higher expression of the gene, was observed with increasing severity of illness from non-SIRS to SIRS. $IL10 G$ allele frequency was increased in patients who died. No association with disease severity was observed.</td>
</tr>
<tr>
<td>*Reid et al, 2002, prospective genetic association, UK</td>
<td>Polymorphisms in the $TNFA$, $TNFB$, $IL10$, and $TGF-\beta1$ genes (88 MODS patients)</td>
<td>The frequency of the different $IL10$ genotypes (corresponding to high, intermediate, and low $IL10$ production) were significantly different between controls and MODS patients. High $IL10$ producers were underrepresented in the MODS group (6% vs 30%). No relationship between genotype and mortality.</td>
</tr>
<tr>
<td>Jaber et al, 2004, prospective genetic association, USA</td>
<td>$-1082$ A/G (and $TNFA -308$ G/A) (61 intermittent hemodialysis patients)</td>
<td>The $-1082$ G allele was associated with a lower risk of death after adjustment for the MOF score (HR = 0.36). The $TNFA$ high and $IL10$ low producer genotype was associated with a 6-fold increased risk of death compared to the $TNFA$ low and $IL10$ intermediate/high producer genotype.</td>
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<tr>
<td><strong>IL1RN Gene Polymorphisms</strong></td>
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</tr>
<tr>
<td>Arnalich et al, 2002,(^{12}) case-control genetic association, Spain</td>
<td>2 repeats at intron 2 (IL1RN2) (78 severe sepsis patients, 130 healthy controls and 56 patient controls)</td>
<td>Significant association between IL1RN polymorphism and survival. Homozygotes for the allele had a 6.47-fold increased risk of death (95% CI: 1.01–41.47). Compared with patients homozygous or heterozygous for the allele 1, IL1RN2 homozygotes produced lower induced levels of IL1RN.</td>
</tr>
<tr>
<td>*Fang et al, 1999,(^{10}) prospective, consecutive entry, Germany</td>
<td>A2 (2 repeats) (and IL1B TaqI and TNFB NcoI (TNFB2) polymorphism) (93 severe sepsis patients and normal controls)</td>
<td>Frequency of the allele IL1RNA2 was increased in patients. No association with outcome. No significance for the IL1B TaqI polymorphism. TNFB2 was associated with nonsurvival.</td>
</tr>
<tr>
<td>*Ma et al, 2002,(^{48}) prospective consecutive entry genetic association, China</td>
<td>VNTR (86 bp, intron 2: RN2) and A2 (2 repeats) (and TNFB2 NcoI at –511) (77 severe sepsis patients and normal controls)</td>
<td>Genotypes A2/2, B2/2, and RN2/2 were associated with higher mortality (70%–80%) in septic patients. Patients with any 2 of the alleles (ie, A2, B2, RN2) suffered from more severe sepsis and higher mortality (55%–65%). Septic patients with genotypes A1/1, B1/1, and RN1/1 had lower mortality (0%–13%).</td>
</tr>
<tr>
<td><strong>TLR4 Gene Polymorphisms</strong></td>
<td></td>
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</tr>
<tr>
<td>Agnese et al, 2002,(^{47}) genetic association, USA</td>
<td>Mutations Asp299Gly and Thr399Ile (77 SIRS patients, 39 volunteers)</td>
<td>Variants present in 18% of patients and in 13% of volunteers. Higher incidence of gram (−) infection in patients with mutations.</td>
</tr>
<tr>
<td>Lorenz et al, 2002,(^{47}) genetic association, USA</td>
<td>Mutations Asp299Gly and Thr399Ile (91 septic shock patients, 73 healthy controls)</td>
<td>Asp299Gly allele found exclusively in septic shock patients. Patients with Asp299Gly/Thr399Ile alleles had a higher prevalence of gram (−) infections.</td>
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<td>*Barber et al, 2004, genetic association, USA</td>
<td>896 A/G (and CD14 – 159, TNFA – 308, IL1B – 31, IL6 – 174) (159 burn patients)</td>
<td>Carriage of TLR4 896 G allele imparted increased risk of severe sepsis, relative to AA homozygotes (OR: 6.4; 95% CI: 1.8–23.2). No association with mortality.</td>
</tr>
<tr>
<td>Lorenz et al, 2000, genetic association, USA</td>
<td>Arg753Gln (91 septic patients)</td>
<td>The polymorphism occurred in 2 patients, who both had staphylococcal infections.</td>
</tr>
<tr>
<td>*Sutherland et al, 2005, genetic association, Canada</td>
<td>16933 T/A (and CD14 C-159 T, MBL X/Y and B, C, and D polymorphisms) (252 SIRS patients)</td>
<td>16933 AA allele associated with increased prevalence of sepsis and with gram-positive bacteria. No association with septic shock or survival.</td>
</tr>
<tr>
<td>Gibot et al, 2002, case-control genetic association, France</td>
<td>−159 C/T (90 septic shock patients, 122 matched controls)</td>
<td>−159 TT allele associated with increased prevalence of positive bacterial cultures and with gram-negative bacteria. No association with septic shock or survival.</td>
</tr>
<tr>
<td>D’Avila et al, 2006, prospective genetic association, Brazil</td>
<td>260 C/T (85 critically ill patients)</td>
<td>The T allele and TT genotype were overrepresented among septic shock patients. The mortality of patients with TT genotype (71%) was higher than in patients with other genotypes (48%). The TT genotype was independently associated with risk for death (OR: 5.30; 95% CI: 1.20–22.50).</td>
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<td><strong>MBL Gene Polymorphisms</strong></td>
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<tr>
<td>Garred et al, 2003, prospective genetic association, Denmark</td>
<td>–221 G/C (X/Y) and exon 1 B, C, D polymorphisms (272 SIRS patients)</td>
<td>Presence of variant alleles associated with occurrence of sepsis, severe sepsis, and septic shock, as well as increased risk for death.</td>
</tr>
<tr>
<td>*Sutherland et al, 2005, genetic association, Canada</td>
<td>–221 G/C (X/Y) and exon 1 B, C, D polymorphisms (and TLR2 16933 T/A, CD14 C/T (252 SIRS patients)</td>
<td>MBL haplotype pairs XO/O and O/O associated with increased prevalence of positive bacterial cultures. No association with septic shock or survival.</td>
</tr>
<tr>
<td>Gordon et al, 2006, prospective genetic association, UK</td>
<td>–221 G/C (X/Y) and exon 1 B, C, D polymorphisms (174 severe sepsis patients, normal controls)</td>
<td>Exon 1 polymorphisms more frequent in patients (54.6% vs 39.7%). Significant difference in haplotype frequency compared to controls. No association with survival.</td>
</tr>
<tr>
<td>Fidler et al, 2004, prospective genetic association, UK</td>
<td>Exon 1 B, C, D polymorphisms (100 pediatric ICU patients with ≥1 organ failures)</td>
<td>The variant alleles were overrepresented in patients who developed SIRS. Genotype associated with MBL serum levels.</td>
</tr>
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<td><strong>HSP Gene Polymorphisms</strong></td>
<td></td>
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</tr>
<tr>
<td>*Waterer et al, 2003, prospective genetic association, Australia</td>
<td>HSP70-2 gene: 1267 A/G (and TNFβ 250 G/A) (343 community-acquired pneumonia patients)</td>
<td>HSP70-2 1267AA genotype was the strongest predictor of septic shock (RR: 3.5). The greater risk of septic shock was associated with carriage of HSP70-2 1267 A/T TNFβ 250 A haplotype.</td>
</tr>
<tr>
<td>Shröder et al, 2003, prospective genetic association, Germany</td>
<td>HSPA1B gene: 1538 G/A, HSPA1L gene: 2437 C/T (80 severe multiple trauma patients)</td>
<td>Genotypes HSPA1B AG or HSPA1L CT associated with higher plasma concentrations of TNFα and IL6 compared with genotype GG or TT. Presence of the HSPA1L genotype CT was a risk factor for liver failure (OR: 4.6; 95% CI: 1.5–14.1) and multiple organ dysfunction (OR: 3.0; 95% CI: 1.1–9.2).</td>
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<tr>
<td>Geishofer et al, 2005,(^{152}) prospective, multicentre genetic association, Austria</td>
<td>(4G/5G) insertion/deletion (347 children with meningococcal infection, controls)</td>
<td>Mortality was significantly associated with the (4G/4G) genotype (OR: 2.31). Sepsis was more frequent in carriers of the (4G/4G) genotype (OR: 2.21). No association with meningitis.</td>
</tr>
<tr>
<td>Haralambous et al, 2003,(^{153}) case-control study and family-based transmission study, UK</td>
<td>(4G/5G) insertion/deletion (510 pediatric patients, 210 parents of patients, and 155 controls)</td>
<td>Carriage of variant alleles (genotype and frequency) was associated with increased mortality. 40% and 91% reduction in the odds of dying if a patient was either (4G/5G) or (5G/5G), respectively. In survivors, the (4G/4G) genotype associated with vascular complications (RR: 2.4; 95% CI: 1.1–5.0).</td>
</tr>
<tr>
<td>Hermans et al, 1999,(^{151}) genetic association, Netherlands, UK</td>
<td>(4G/5G) insertion/deletion (175 children with meningococcal disease, 226 controls)</td>
<td>Patients with the (4G/4G) genotype had higher PAI1 concentrations than those with the (4G/5G) or (5G/5G) genotype, and had an increased risk of death (RR: 2.0, 95% CI: 1.0–3.8).</td>
</tr>
<tr>
<td>Westendorp et al, 1999,(^{154}) genetic association, Netherlands</td>
<td>(4G/5G) insertion/deletion (50 survivors of meningococcal infection, 131 controls, 183 first-degree relatives of patients with meningococcal infection)</td>
<td>Allele frequencies were similar between patients and controls. (4G/4G) genotype was present in 9% of relatives of meningitis patients (vs 36% of those with septic shock). Patients whose relatives were carriers of the (4G/4G) genotype had higher risk of septic shock (OR: 5.9; 95% CI 1.9–18.0).</td>
</tr>
<tr>
<td>Zhan et al, 2005,(^{155}) case-control genetic association, China</td>
<td>(4G/5G) insertion/deletion (89 sepsis patients, matched patients without sepsis)</td>
<td>(4G/4G) genotype and the (4G) allele were more frequent in sepsis patients and in nonsurvivors, compared with survivors.</td>
</tr>
<tr>
<td>Menges et al, 2001,(^{157}) genetic association, Netherlands, UK</td>
<td>(4G/5G) insertion/deletion (61 severely injured patients)</td>
<td>58% patients with genotype (4G/4G) did not survive, whereas 28% of patients with heterozygous genotype (4G/5G) and 15% of patients with genotype (5G/5G) died.</td>
</tr>
<tr>
<td>Author(s), Year, Type of Study, Country of Origin</td>
<td>Polymorphisms Studied (Subjects)</td>
<td>Summary of Significant Results ($P &lt; .05$)</td>
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<td>-------------------------------------------------</td>
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<td>-----------------------------------------</td>
</tr>
<tr>
<td><strong>Factor V Gene Polymorphisms</strong></td>
<td></td>
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</tr>
<tr>
<td>Yan and Nelson, 2004, prospective genetic...</td>
<td>506 Arg/Gln (FV Leiden) (3894 adults with severe sepsis)</td>
<td>9% of patients with severe sepsis were heterozygous carriers. The proportion of FV Leiden carriers in patients with severe sepsis differed slightly from that predicted.</td>
</tr>
<tr>
<td>Benfield et al, 2005, prospective cohort study,</td>
<td>506 Arg/Gln (FV Leiden) (9253 individuals)</td>
<td>In subjects hospitalized for sepsis, FV Leiden carriers were at an increased risk for 28-day mortality after admission (RR: 4.41; 95% CI: 1.42–13.67).</td>
</tr>
<tr>
<td>Kondaveeti et al, 1999, genetic association, UK</td>
<td>506 Arg/Gln (FV Leiden) (259 children with meningococcal disease, 80 healthy controls, 79 parents of children with fatal meningococcal disease)</td>
<td>No difference in the frequency of FV Leiden among groups. Heterozygous patients had increased complications. Among survivors, heterozygocity for FV Leiden associated with risk of complications (RR: 3.1; 95% CI: 1.2–7.9).</td>
</tr>
<tr>
<td><strong>TAFI Gene Polymorphisms</strong></td>
<td></td>
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</tr>
<tr>
<td>Kremer Hovinga et al, 2004, genetic association, Netherlands</td>
<td>Thr325ile dimorphism (50 survivors of meningococcal disease, 176 first-degree relatives of patients with meningococcal disease, 212 controls)</td>
<td>The 325 Ile/Ile genotype was more common among nonsurvivors (19.2%). Patients of parents with the TAFI 325 Ile/Ile genotype had a 1.6-fold (95% CI: 0.7–3.7) higher risk for meningococcal disease and a 3.1-fold (95% CI: 1.0–9.5) increased risk for mortality.</td>
</tr>
</tbody>
</table>

Studies exploring polymorphisms in multiple factors appear more than once and are noted by an asterisk (*). Owing to the large amount of data, studies that did not support an association are not included, although many of them are methodologically sound. (Gene Loci preceded by “–” are at the promoter region of the gene. ARDS indicates acute respiratory distress syndrome; CI, confidence interval; HR, hazard ratio; HSP, heat shock protein; IL, interleukin; MBL, mannose-binding lectin; MODS, multiple organ dysfunction syndrome; MOF, multiple organ failure; OR, odds ratio; PAI-1, plasminogen activator inhibitor–1; RA, receptor antagonist; TAFI, thrombin-activatable fibrinolysis inhibitor; PBMC, peripheral blood mononuclear cells; RR, risk ratio; TGF, transforming growth factor; TLR, toll-like receptor; TNF, tumor necrosis factor; VNTR, variable number tandem repeats.)
and practice of individualized care. Finally, a preliminary theoretical framework for incorporation of genetic variations into individualized care planning based on complexity theory will be proposed. A glossary of the terms used in this article is listed in Table 2.

The pathophysiology of sepsis is multifaceted, primarily involving altered cellular signaling due to unprecedented levels of circulating cellular mediators, which contribute to dysregulation of immunity, tissue repair, coagulation, and cellular stress responses. These highly integrated and complex processes depend on multidirectional links among most organ systems and cell types. They, therefore, constitute a multifactorial chaotic system, highly sensitive to subtle changes with unpredictable outcomes. Genomic research in sepsis aspires to pinpoint some of these subtle disparities in the circumstances of individuals that may, if not properly addressed, have significant impact on their well-being and survival when challenged by infectious agents. Herein, SNPs are represented by the initials of the nucleotides and the gene site involved, for example, a 208 G/A SNP denotes that the common allele form, at 208 bp of the gene, contains guanine (G), which is substituted by adenine (A) at the rare (polymorphic) allele. Likewise, polymorphic alleles are named with the initial of the nucleotide they carry: A, G, T (thymine), or C (cytosine).

A Comment on Methodology of Genetic Association Studies in Sepsis

Genotype association studies in sepsis are proliferating; nonetheless, the exploration of the association of polymorphisms with the incidence and outcome of sepsis has often provided conflicting results. Peters et al. through a systematic review and secondary analysis of banked genetic material highlighted that common methodological errors may lead to failure to confirm genotype, thus jeopardizing the validity of studies. Furthermore, a number of methodological limitations (sampling method, sample size, multiple confounding variables, inadequate statistical models, low reliability of methods, inadequate case-control matching) evident in many of these studies may limit generalizability and internal validity, thus rendering the inference of relationships between allelic variations and clinical outcome problematic. In addition, hard evidence suggests that some of the alleged pathogenetic polymorphisms may not be functional, leading to the conclusion that significant polymorphisms may still elude detection obscured by their less important linkage disequilibrium counterparts. Indeed, following a systematic evaluation of genetic association studies in human diseases, Bogardus and colleagues concluded that many of these attempts failed to follow standard rules of epidemiological research methodology, in accordance with a recent meta-analysis.

An additional confounder lies at the different ethnic backgrounds of the populations studied. Polymorphisms may exhibit significant interethnic variability; therefore, genetic association results may not be easily transferable across different ethnicities. In addition, factors already known to affect outcome, such as age, gender, comorbidities, type of organism and site of infection need to be taken into account. Furthermore, individuals may carry multiple allelic polymorphisms, either by chance or due to linkage disequilibrium, which may act as major confounders. Vitali and Randolph provide a comprehensive summary of methodological standards for case-control genetic association studies. Nonetheless, even well-designed studies exhibiting associations of SNPs with sepsis cannot establish causality. More investigation is needed in order to elucidate some of these complex multivariate associations in a way that may be proven meaningful clinically. Our increased awareness of the multiple simultaneous, often nonlinear, interactions in sepsis, will probably render some of our traditional statistical modeling approaches obsolete. Extended multidisciplinary efforts may be needed to decipher the role of genetic makeup in sepsis.

Cellular Messenger Polymorphisms

Cytokines are peptides produced by diverse types of cells (including immune, endothelial and nervous cells), which act as cell-to-cell messengers to regulate diverse processes, including immunity, inflammation, and cellular response to adverse conditions. Cytokines account for the high level of integration of inflammatory responses, including bidirectional links with the CNS, endothelia and organ system responses. Cytokine polymorphisms have been implicated in the pathogenesis of many diverse disease states. Genetic variations in
### Table 2: Glossary

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Allele</td>
<td>Alternative forms of a genetic locus; a single allele for each locus is inherited from each parent separately</td>
</tr>
<tr>
<td>Apoptosis</td>
<td>Programmed cell death, the body’s normal method of disposing of unwanted, or unneeded, cells</td>
</tr>
<tr>
<td><strong>CD14</strong></td>
<td><em>CD14</em> is a surface protein preferentially expressed on monocytes/macrophages. It binds lipopolysaccharide binding protein and, recently, it has been shown to bind apoptotic cells</td>
</tr>
<tr>
<td>Exon</td>
<td>The protein-coding DNA sequences of a gene</td>
</tr>
<tr>
<td>Genome</td>
<td>All the DNA contained in an organism or a cell, which includes both the chromosomes within the nucleus and the DNA in mitochondria</td>
</tr>
<tr>
<td>Genotype</td>
<td>The genetic identity of an individual that does not show as outward characteristics</td>
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<tr>
<td>Haplotype</td>
<td>Set of genes at more than 1 locus, which is inherited from one of the parents</td>
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<tr>
<td>Haplotype clade</td>
<td>Set of genes that has branched from a specific ancestor haplotype and may have been altered through time because of various recombination events</td>
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<td>Heat shock proteins</td>
<td>HSPs, also called stress proteins, are induced under cellular stress conditions, such as oxygen deprivation, oxidative stress, temperature elevation, and cytokine stimulation. Also, they are involved in protein folding and protection from damage</td>
</tr>
<tr>
<td>Homozygous</td>
<td>Possessing 2 identical forms of a particular gene, 1 inherited from each parent</td>
</tr>
<tr>
<td>Intron</td>
<td>A segment of DNA (between exons) that is transcribed into nuclear RNA, but is removed in the subsequent processing into mRNA</td>
</tr>
<tr>
<td>In vitro</td>
<td>An experimental situation outside the organism. Biological or chemical work done in the test tube (literally, in glass) rather than in living systems</td>
</tr>
<tr>
<td>In vivo</td>
<td>An experimental situation inside the organism. Experimental subjects are living systems</td>
</tr>
<tr>
<td><strong>IRAK4</strong></td>
<td>Interleukin-1 receptor-associated kinase 4</td>
</tr>
<tr>
<td>Kinase</td>
<td>An enzyme that transfers a phosphate group from ATP to another molecule</td>
</tr>
<tr>
<td>Linkage disequilibrium</td>
<td>A condition where alleles occur together more often than can be accounted for by chance. Indicates that the 2 alleles are physically close on the DNA strand</td>
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<tr>
<td><strong>MD2</strong></td>
<td>A molecule that confers lipopolysaccharide responsiveness on toll-like receptor 4</td>
</tr>
<tr>
<td>Monoclonal antibody</td>
<td>The unique immunoglobulin molecule (antibody) produced by a clone of B lymphocytes</td>
</tr>
<tr>
<td><strong>NF-κB</strong></td>
<td>Rel or NF-kappaB (<em>NF-κB</em>) proteins comprise a family of structurally related eukaryotic transcription factors that are involved in the control of a large number of normal cellular and organismic processes, such as immune and inflammatory responses, developmental processes, cellular growth, and apoptosis</td>
</tr>
<tr>
<td>Pathogen-associated molecular patterns</td>
<td>PAMPs are small molecular sequences consistently found on pathogens. They are recognized by toll-like receptors and other Pattern Recognition Receptors (PRRs)</td>
</tr>
</tbody>
</table>

(continues)
the proinflammatory cytokines TNFα, TNFβ, and IL6 and the anti-inflammatory cytokine IL10 are the most extensively studied in relation to sepsis. Remarkably, patients predisposed to produce a balanced anti-, proinflammatory response appear to have better chances for survival in multiple organ dysfunction syndrome (MODS) and sepsis.10

**Tumor Necrosis Factor-α**

Tumor necrosis factor-α (TNFα) is a cardinal mediator of sepsis11 and one of the initial triggers in the activation and regulation of immune responses. Nonetheless, studies examining its levels and association with survival and severity have had conflicting results.12 Recent evidence suggests that TNFα gene variations may in part predispose patients for increased severity,13 which is sometimes,14,15 but not always,16 associated with altered TNFα levels. In addition, TNFα polymorphisms may occur in linkage with TNFβ variations,17 presumably increasing individual risk for septic shock.18

Many different SNPs have been detected at the promoter region of the TNFα gene,19 of which those relevant to sepsis appear to be –308 G/A, -376 G/A, and -238 G/A transitions.20 The –308 G/A was the first to be identified and the most widely studied.21 The common allele form (TNF1) contains guanine (G), and the uncommon one (TNF2) adenine (A).22 However, evidence suggests that the TNF2 polymorphism may not be functional,23,24 in contrast to in vitro studies that showed increased TNFα production.25,26 Evidence on the rest of the TNFα polymorphisms is controversial.11

The significance of the –308 G/A TNFα SNP has been demonstrated through increased detection of the TNF2 allele and an associated increased risk for death in French and Australian medical ICU patients with sepsis,11,27 as well as in North American trauma/surgical ICU patients,18,29 although the association with mortality was not always significant. Furthermore, increased frequency of the TNF2 allele, which was associated with increased mortality and uncontrollable IL6 levels was reported in a mixed group of Japanese critically ill individuals,30 while in Swedish cardiac surgery patients it was associated with higher peak TNFα and IL6 levels and increased risk for multiple organ dysfunction.31 In acute respiratory distress syndrome patients, the TNF2 allele was associated with increased mortality.17

However, recent studies failed to show significant associations of TNFα polymorphisms with either disease severity, susceptibility to sepsis or patient outcomes in white and Chinese adults,14,32–35 and Hungarian septic infants.36 In addition, no association was detected with pancreatitis-related sepsis in 2 Chinese studies.23,37 Nevertheless, methodological limitations, such as small convenience samples and univariate analyses may have limited the validity of these results. In addition, evidence that the TNF2 allele was associated with increased risk for septic shock only when accompanied by a TNFβ polymorphism27 suggests

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**Table 2: Glossary (Continued)**

<table>
<thead>
<tr>
<th>Polymorphisms</th>
<th>Natural variations in a gene, or DNA sequence, so that at least 2 alleles (alternative forms of a DNA locus) are present</th>
</tr>
</thead>
<tbody>
<tr>
<td>Promoter</td>
<td>A site on DNA to which RNA polymerase will bind and initiate transcription.</td>
</tr>
<tr>
<td>SNPs</td>
<td>Allelic variations in a single base pair. Variations occurring at the promoter region of a gene are labeled with a “−” sign, eg, a -208 SNP means that a polymorphism occurs 208 bp before the start codon</td>
</tr>
<tr>
<td>TIR</td>
<td>Toll/interleukin-1 receptor (TIR) domain is the conserved intracellular domain of the 2 families of receptors. It is believed that a TIR domain signaling complex is formed between the receptor and the adapter TIR domains</td>
</tr>
<tr>
<td>Toll-like receptor</td>
<td>Toll-like receptors (TLRs) are type I transmembrane proteins involved in innate immunity by recognizing microbial conserved structures</td>
</tr>
<tr>
<td>VNTR</td>
<td>Variable-number tandem repeats: any gene the alleles of which contain different numbers of repeated oligonucleotide sequences</td>
</tr>
</tbody>
</table>
that multifactorial models need to be explored in order to clarify the significance of TNF polymorphisms in sepsis.

**Tumor Necrosis Factor-β**

Tumor necrosis factor-β (TNFB or LTA) binds to the same receptor as TNFA, and a number of polymorphisms have been described,\(^\text{18}\) of which the 250 G/A at the first TNFB intron is the one most extensively studied in relation to sepsis.\(^\text{27}\) Kahlke et al.\(^\text{19}\) investigated 160 German patients undergoing major gastrointestinal surgery and concluded that the presence of a length polymorphism at an NcoI restriction fragment (which originates after specific DNA cleavage by the restriction endonuclease NcoI) in the TNFB gene associated with increased risk for postoperative complications at the heterozygous state, and with increased risk for severe complications, sepsis and mortality at the homozygous state, in agreement with previous results.\(^\text{40}\) In addition, the presence of the TNFB A allele was associated with increased risk for cardiac and respiratory dysfunction in 95 Swedish cardiac surgery patients,\(^\text{31}\) and increased mortality in British patients with MODS.\(^\text{10}\) Moreover, homozygocity for the TNFB 250 SNP was associated with increased risk for sepsis after trauma in Dutch patients.\(^\text{35,41}\) However, in a German study of 85 critically ill patients postsurgery no association between the incidence of the TNFB 250 SNP and outcome was observed.\(^\text{42}\) Likewise, the incidence of sepsis, septic shock, and mortality was not increased in patients with systemic inflammatory response syndrome (SIRS) bearing the TNFB 250 SNP in a North American study.\(^\text{34}\) Further confounding any inferences regarding the association of TNFB polymorphisms with sepsis, TNFB SNPs are in linkage disequilibrium with heat shock protein 70 (HSP70) alleles. An adenine at both the 250 TNFB and HSP70A1B 1267 gene sites is associated with greater risk for septic shock after trauma\(^\text{43,44}\) and mortality in severe sepsis.\(^\text{45}\) Therefore, examination of potential linkage disequilibrium occurrences and multifactorial models may be necessary before any inferences for the role of TNFB variability in sepsis can be made.

**Interleukin-1β, Interleukin-1α**

Interleukin-1 (IL1; another central mediator of inflammation) occurs in 2 forms: IL1A and IL1B. An SNP is present at the −511 promoter region of the IL1B gene, which is in linkage disequilibrium with another promoter SNP at −31.\(^\text{46}\) Through a multivariate exploration of 1106 British patients with meningococcal meningitis, the −511 SNP at the promoter of IL1B appeared to contribute to mortality.\(^\text{36}\) However, there was no association between IL1B 3594 C/T SNP and severe acute pancreatitis and ensuing septic shock in a Chinese study,\(^\text{47}\) and between the IL1B 3953 C/T SNP and disease severity in meningococcemia in an Irish study,\(^\text{33}\) as well as between the −511 IL1B promoter SNP and susceptibility to sepsis in a Chinese study,\(^\text{48}\) and in a German study.\(^\text{49}\) However, homozygocity for a specific variable-number tandem repeat (VNTR) at exon 5 of the IL1B gene was associated with increased mortality in Chinese patients with sepsis.\(^\text{48}\)

Less evidence exists on the role of IL1A polymorphisms in sepsis. Polymorphic regions with VNTRs are detected within intron 6 of the IL1A gene. Alleles are designated A1, A2, A3, A4, and A5 on the basis of their relative frequency in healthy populations.\(^\text{45}\) Ma and colleagues\(^\text{48}\) reported that Chinese patients homozygous for a specific intron 6 VNTR of the IL1A gene (A2) are at significantly higher risk for death; nonetheless, they did not observe higher frequency of this allele in patients with sepsis, in contrast to previous results by Fang et al.\(^\text{40}\) in Germans. An additional study failed to show increased incidence of A2 in Spanish patients with sepsis and pneumonia.\(^\text{30}\) In summary, results on the role of IL1 polymorphisms are highly variable, presumably due to the many methodological limitations of association studies, and the diverse ethnic background of the populations studied. At the present state of the art, conclusions on the role of IL1 variability in sepsis must be drawn with great caution.

**Interleukin-6**

Interleukin-6 (IL6) plays a role in lymphocyte stimulation and its levels appear to associate with severity and mortality in sepsis, consistently.\(^\text{51}\) Genotype differences in the IL1, TNFA, and HSP70 genes have been implicated in regulating differential peak IL6 levels in SIRS,\(^\text{30,52,53}\) whereas multiple allelic variations have been detected in the IL6 gene: a −174 G/C at the promoter region, a 1753 G/G, and a 2954 G/C.\(^\text{20}\) The −174 G/C SNP was shown to be functional in vivo in white volunteers; however, no association with the ex vivo IL6

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response was observed in Dutch trauma victims. In a study of 326 German surgical patients, the –174 G/C SNP was found to be associated with survival in sepsis but not with the incidence of sepsis, whereas it was associated with survival in meningococcemia in an Irish study.

Haplotype clades bearing specific SNPs (–174 G/C, –1753 C/G, and –2954 G/C) were reported to associate with mortality and susceptibility to MODS in 228 white patients with SIRS. By reviewing evidence through a candidate gene approach, IL6 was shown to be involved in acute lung injury; however, no association between the –174 G/C SNP and severity of pneumonia was detected in an Irish study. In summary, it is possible that genetic variation at the IL6 gene may contribute to the outcome of sepsis; nonetheless, variable association of specific SNPs with IL6 levels and the potential presence of linkage disequilibrium with several alleles still obscure the clinical significance of these results.

**Interleukin-10**

Interleukin-10 (IL10) appears to be an integral part of the body’s anti-inflammatory processes, since its production is stimulated by inflammation, and it is a potent inhibitor of nonspecific inflammatory responses. In sepsis, high IL10 levels associating with severity have been reported, consistently. Interleukin-10 is highly polymorphic and at least 3 SNPs at the promoter region (–1082, –819, and –592, of which the latter 2 are in linkage disequilibrium) have been implicated in sepsis. Lowe et al explored the incidence and effect of these promoter SNPs, and of 2 dinucleotide repeats in 67 Scottish critically ill patients and 132 volunteers. Presence of the –592 C/A SNP was found to be associated with lower stimulated IL10 release and higher mortality. No association was observed regarding the rest of the polymorphisms. In addition, in a Japanese population, concurrence of the IL10 –592 C/A with the TNFA –308 G/A SNP increased the risk for sepsis. However, in a Canadian study, the 592G/734G/3367G haplotype was found to be associated with increased mortality and organ dysfunction in patients with pulmonary, but not extrapulmonary, sepsis. A G/A substitution at –1082 bp has been associated with severity of meningococcemia in an Irish sample, and with lower ex vivo IL10 production and susceptibility to sepsis. Conversely, it was the IL10 –1082 G allele that appeared to be associated with increased risk for sepsis in Chinese samples, and increased severity of SIRS in an Irish sample. Nonetheless, in an American study of patients with acute renal failure, the IL10 -1082 G allele was associated with lower mortality when adjusting for multiple organ dysfunction severity. The IL10 –1082 G allele has been associated with higher stimulated levels of IL10 in Caucasian critical care patients. Results from a British study support the hypothesis that low IL10 producer genotypes may be implicated in multiple organ dysfunction. In conclusion, evidence on the role of IL10 gene variations in sepsis is highly variable. Ethnicity is an obvious confounder; nonetheless, more well-designed association studies are needed.

**Interleukin-1 Receptor Antagonist**

Interleukin-1 receptor antagonist (IL1RN) antagonizes the proinflammatory actions of IL1A and IL1B by binding to their receptor. Variable-number tandem repeats have been described in the IL1RN gene. Arnalich et al evaluated the presence of 5 different VNTRs of various sizes at the IL1RN intron 2 in Spanish patients with severe sepsis, and concluded that homozygosity for 2 repeats of 250 bp associated with higher mortality (after adjusting for APACHE II scores), and lower ex vivo IL1RN production. Similarly, in Chinese populations, the same VNTR allele was associated with increased susceptibility to and severity of sepsis. Hence, although not as extensively studied, IL1RN polymorphisms may be promising candidates for genetic associations in sepsis; nonetheless, they should be explored in relation to the rest of IL1 peptides.

Some evidence exists for other cytokine polymorphisms as well, including the proinflammatory IL18, interferon-γ, and pre-B-cell colony-enhancing factor. Nonetheless, owing to the absence of sufficient investigation, such results should be considered preliminary.

**Pathogen Recognition/Signaling Molecule Polymorphisms**

Toll-like receptors (TLRs) are transmembrane receptors, expressed primarily on immune and epithelial cells, that recognize pathogen-associated molecular patterns (PAMPs), thus initiating and sustaining the inflammatory response. They constitute the major mechanism...
for microorganism detection, and initiate a little understood complex cascade of kinases and multiple adapter molecules. Recognition of PAMPs often requires the presence of accessory molecules such as CD14 or MD2. Toll-like receptors exhibit some specificity in pathogen recognition: TLR2 appears to be involved in recognition of gram-positive and TLR4 in recognition of gram-negative bacteria. Pathogen-associated molecular patterns recognition takes place either at an extracellular or at an intracellular domain. Following PAMP recognition, intracellular signaling is carried out through a cytoplasmic domain (TIR), which through recruitment of specific intracellular proteins (e.g., MyD88, TIRAP/MAL, TRAM, TRIF) enhances translocation of the transcriptional activator NF-kappaB (NF-kB) into the nucleus, thus promoting the expression of specific cytokines and other pertinent molecules. Two of the 10 TLRs identified in humans have been explored in relation to the genetics of sepsis: TLR2 and TLR4, the latter of which is the most widely investigated, along with the accessory molecule CD14.

**Toll-like Receptor 4**

Preliminary evidence for the role of TLR4 in sepsis was provided by animal studies demonstrating that the long-known hypo-responsiveness of a common laboratory mouse strain (C3H/HeJ) to endotoxin (lipopolysaccharide [LPS], cell-wall component of gram-negative bacteria) was attributed to a mutation in the TLR4 gene. Furthermore, Arbour and colleagues showed that 2 common SNPs at the TLR4 gene (896 A/G, or Asp299Gly, and 1196 C/T, or Thr399Ile) account for attenuated in vivo responses to inhaled endotoxin and for in vitro hyporesponsiveness of immune and airway epithelial cells in humans. The 896 A/G SNP appears to be quite common in whites, but it may be less frequent among individuals of Asiatic descent. However, monocytes of individuals bearing this G allele showed no deficit in LPS signaling, probably suggesting the existence of alternative molecules and/or signaling pathways, thus undermining the clinical significance of these SNPs in sepsis. Nonetheless, an association with the incidence of gram-negative infection and the susceptibility to septic shock in North American critical care patients, and a potential trend for higher mortality in a UK critical care patient population have been reported. Similarly, in North American burn victims, the 896 A/G SNP imparted an increased risk for severe sepsis, after adjustment for clinical parameters, gender, and ethnicity. Nevertheless, no association between the 896 A/G SNP (G allele) and risk for meningococcal disease were observed in a British sample and a Gambian pediatric sample. In summary, the hypothesis that genomic variations in the TLR4 gene predispose individuals for sepsis, along with the possible mechanisms that mediate altered immunity, merits further exploration.

**Toll-like Receptor 2**

Toll-like receptor 2 (TLR2) appears to be involved in staphylococcus signaling; however, studies examining susceptibility to *Staphylococcus aureus* infections in the presence of 2 common TLR2 SNPs in whites had conflicting results. However, a –16933 T/A SNP was associated with increased incidence of positive cultures and gram-positive bacteria in a Canadian population of SIRS patients.

**CD14**

CD14 is a ubiquitous pattern recognition receptor, specific for LPS and a variety of other ligands, expressed primarily on immune and endothelial cells, the gene of which exhibits considerable interethnic variability. It acts as a coreceptor for TLR4, and a soluble form (sCD14) is shed by monocytes to facilitate LPS signaling for all other cells. Two polymorphisms at the promoter region of the CD14 gene (–159 C/T and -260 C/T) are the most widely explored in inflammatory diseases. The –159 C/T SNP (T allele) has been associated with increased detection of both membrane-bound CD14 on monocytes and circulating levels of CD14; nonetheless, the role of both SNPs in the pathogenesis of sepsis remains unclear.

In a Canadian study, the –159 C/T SNP (T allele) was associated with increased prevalence of gram-negative infections and sepsis, but not with the prevalence of septic shock or survival. Likewise, in a French multicenter study, an association with mortality was reported. Nonetheless, in a North American ICU population Agnese et al did not observe any association between CD14 SNPs and incidence of infection, and in a Japanese sample no association with sepsis was observed. Similarly, in a German study exploring 204 patients with severe sepsis and 247 controls, no
association between the –159 C/T SNP and sepsis was detected.\textsuperscript{101} Furthermore, Zhang et al\textsuperscript{17} reported no association between the –159 C/T SNP and severe acute pancreatitis and septic shock, and Barber et al\textsuperscript{19} no association with sepsis in burn trauma.

Recently, the –260 C/T CD14 SNP (T allele) has been linked to increased survival in critically ill patients in a Southern Brazilian population.\textsuperscript{102} The –260 C/T SNP has also been implicated in atherogenesis and cardiovascular events.\textsuperscript{103} Furthermore, although evidence on the role of CD14 is conflicting, clinical studies are exploring the efficacy of a chimeric monoclonal antibody (IC14) against human CD14 in patients with severe sepsis.\textsuperscript{104}

**Mannose-binding Lectin**

Mannose-binding lectin (MBL) is a circulating serum protein that recognizes and binds carbohydrate structures on the surface of infectious agents and activates the complement system through MBL-associated serine proteases.\textsuperscript{105} Interindividual differences of serum MBL are mainly caused by structural variant alleles in the MBL gene,\textsuperscript{106} and MBL deficiency has been linked to increased risk of infections in early childhood\textsuperscript{107} and of sepsis in critically ill adults.\textsuperscript{108} Point mutations at exon 1 resulting in 4 different variant alleles, and an SNP at the promoter region –221, have been described.\textsuperscript{109,110} In a Danish study, the presence of MBL variant alleles and promoter alleles was associated with the development of sepsis, severe sepsis, septic shock, and mortality in 272 patients with SIRS,\textsuperscript{111} and it was suggested that substitution therapy may be tested for sepsis prophylaxis. Similarly, Sutherland et al\textsuperscript{19} reported that the presence of MBL alleles was associated with increased risk for positive bacterial cultures. Furthermore, in British patients, the presence of variant alleles was associated with susceptibility to sepsis and septic shock in 174 adult patients with sepsis,\textsuperscript{109} and with low levels of MBL, and increased risk of SIRS, sepsis, and septic shock in 100 critically ill children.\textsuperscript{112} Nonetheless, in a random sample of 141 adult Danish patients with cultures positive for *Streptococcus pneumoniae*, no association with susceptibility to sepsis and patient outcomes was observed.\textsuperscript{111} In summary, preliminary evidence potentially supports a role for MBL polymorphisms in sepsis susceptibility; nonetheless, further investigation is needed to replicate these findings in different populations.

Genetic polymorphisms involving the Fcγ (FCG) leukocyte receptors, which are involved in opsonization and phagocytosis of bacteria, may also be significant in sepsis. Polymorphisms in the FCGR2A and FCGR3B receptors have been linked to increased susceptibility to meningococcal disease,\textsuperscript{113,114} and to meningococemia-related sepsis and shock.\textsuperscript{116,117} Nonetheless, the association of FCG polymorphisms with nonmeningococcal sepsis is unclear.

**Intracellular Signaling Molecules**

Following TLR engagement, defects of the pathway for the translocation of the transcription factor NF-κB into the nucleus to initiate expression of inflammatory mediators may alter individual susceptibility to infection. The IL1 receptor-associated kinase-4 (IRAK4) is an intracellular kinase that transduces intracellular signals conveyed by the TLRs and IL1 receptors.\textsuperscript{118} Three human immunodeficiencies associated with impaired TLR signaling have been described, which are linked with developmental defects.\textsuperscript{119} Patients with IRAK4 deficiency are at increased risk for invasive disease due to pyogenic bacteria,\textsuperscript{120} but present no developmental defects. Homozygocity for either of the 2 variant alleles appears to inhibit expression of IRAK4 in humans, thereby inhibiting activation of NF-κB,\textsuperscript{121} which is in particular involved in LPS signaling.\textsuperscript{122} The presence of a newly characterized splice variant of IRAK4 (IRAK1c), which inhibits NF-κB activation,\textsuperscript{123} adds further complexity to the intracellular signaling system of pathogens. No genetic association studies for this intracellular pathway in septic patients have been located.

**Programmed Cell Death Polymorphisms**

Widespread triggering of apoptosis, at least in lymphoid tissues, has been implicated in the pathophysiology of MODS and sepsis,\textsuperscript{124,125} however, the association with nonlymphoid tissue apoptosis is less compelling.\textsuperscript{126} Apoptotic loss of immunocytes may contribute to the immunological derangements, and hyporeactivity observed in sepsis and MODS,\textsuperscript{127} whereas neutrophil resistance to apoptosis appears to promote neutrophil aggregation and subsequent microcirculatory and oxidative damage.\textsuperscript{128,129} Moreover, in vivo silencing of pro-apoptotic genes appears to rescue septic mice.\textsuperscript{130} Apoptosis-related polymorphisms have been studied extensively in relation to
cancer susceptibility (eg, Wu et al); nonetheless, the investigation of variations in apoptotic genes in sepsis is very limited. Caspaces mediate proteolysis in inflammation and intracellular apoptotic signaling. An SNP in the human caspase-12, detected in individuals of African descent, has been implicated in hyperresponsiveness to LPS, but not with alterations in apoptotic sensitivity. Polymorphisms in the gene of the apoptotic receptor Fas have been associated with the severity of hepatitis C in humans, and apoptotic gene polymorphisms with the response to Salmonella enteritidis in poultry. Given the presence of multiple SNPs in apoptotic pathway genes in humans, their involvement in sepsis merits investigation.

**Cellular Stress-Protein Polymorphisms**

Heat shock proteins (HSP) are phylogenetically primitive proteins that are expressed in response to cellular stress and are involved in diverse responses including cellular dormancy and protein repair. Some HSPs are expressed constitutively in nonstressed cells and they are essential for protein compilation and generation of protective cellular responses. In animal models of sepsis, induction of HSPs reduces organ dysfunction and mortality. In patients with severe sepsis, the heat shock response appears to be activated, and an impairment of the ex vivo LPS-inducible 70-kD HSP (HSP70) expression in lymphocytes was observed, which may be implicated in immune dysfunction. There are 3 adjacent genes in the HSP70 family: HSPA1A, HSPA1B, and HSPA1L, of which the first 2 encode the same and the third one a highly homologous protein. Waterer et al reported that homozygosity for a polymorphism in HSPA1B (1267 G/A) was a strong predictor of septic shock in patients with community-acquired pneumonia. However, Schroeder et al detected no association between 2 biallelic polymorphisms in HSPA1A and HSPA1B and the susceptibility or outcome of sepsis. Nonetheless, although the HSPA1B 1267 A/G SNP is silent, it is in linkage disequilibrium with a HSPA1B –179 C/T polymorphism that accounts for lowered production of HSP70, and therefore may be involved in susceptibility to sepsis. Moreover, polymorphisms in HSPA1B and HSPA1L and TNFA and IL6 concentrations, respectively, as well as the outcome of severe injury were found to be associated in a German study. In summary, evidence on the role of HSP polymorphisms in sepsis is scarce, implying the need for further investigation.

**Coagulation Protein Polymorphisms**

Activation of coagulation, a response integrated with inflammatory triggering, is a key pathogenetic event in sepsis. Increased coagulability, along with decreased fibrinolysis and consumption of coagulation inhibitors lead to fibrin deposition in the microvasculature. Abnormalities in the antithrombin III, activated protein C (APC), and tissue-factor inhibitor pathways have been implicated in the pathogenesis of sepsis, and administration of recombinant human APC appears to be effective for the reduction of mortality in clinical trials with patients with severe sepsis. A plethora of studies focused on the role of hemostatic gene polymorphisms in cardiovascular diseases and provided worth noticing associations, but, most likely, moderate evidence.

**Plasminogen Activator Inhibitor-1**

Plasminogen activator inhibitor-1 (PAI1) is involved in inhibition of both tissue- and urokinase-type plasminogen activators, promoting the stability and extension of the clot and increasing clot resistance to lysis, and acts as an acute-phase protein in inflammation. Increased expression of PAI1 is considered as a risk factor in cardiovascular disease, and may associate with survival in meningococcal septic shock. The functional 4G/5G insertion/deletion polymorphism at –675 of the promoter region is the one most extensively investigated in sepsis. Individuals homozygous for the 4G allele have significantly higher plasma activity of PAI1 compared to 5G homozygotes. In a multicenter study exploring 347 Central European and British children with systemic meningococcemia, the homozygous 4G/4G genotype conferred a greater risk for sepsis (odds ratio [OR] = 2.21) and mortality (OR = 2.31), although there was no association with the probability of meningitis. Likewise, in a case-control study of British children with meningococcal disease, an increased risk for death (OR = 1.9), death from sepsis (OR = 2.7), and increased risk for vascular complications in survivors (OR = 2.4) were observed in 4G/4G homozygotes.
These results are in accordance with a previous study of Dutch and British children.\textsuperscript{151} In a Dutch study of patients with meningitis, presence of the 4G/4G allele in relatives of diseased patients was associated with increased risk for septic shock (OR = 5.9), although there was no association with the susceptibility to meningitis.\textsuperscript{154} Likewise, in a smaller Chinese study, the 4G/4G genotype was associated with greater risk for sepsis from all causes and mortality,\textsuperscript{155} similar to the results in a recent Turkish study.\textsuperscript{156} Moreover, poorer survival after severe injury has been associated with the 4G/4G genotype.\textsuperscript{157} In summary, the evidence reviewed herein suggests an association of PAI1 genotypes and outcome of sepsis, especially meningococcal sepsis, and may be of great importance for pediatric critical care.

**Factor V**

Polymorphisms in the factor V (FV) gene may interfere with its proteolytic degradation by APC through altering proteolytic sites, thus rendering factor Va partially resistant to inactivation by APC. Commonly (5\% of whites, approximately), but with significant ethnic heterogeneity,\textsuperscript{158} 1691 A/G SNP in the factor V gene (FV Leiden) has been implicated in the pathogenesis of sepsis. The high prevalence of FV Leiden in certain populations has prompted the hypothesis that this SNP may confer some evolutionary advantage. Studies with mutant FV Leiden mice showed increased survival following septic challenges.\textsuperscript{159,160} Furthermore, secondary analysis of data of patients involved in a multicenter clinical trial of APC revealed a trend for increased survival following APC administration and for decreased susceptibility to sepsis in FV Leiden carriers.\textsuperscript{161} Nonetheless, in a Danish prospective cohort study of 9253 individuals, although heterozygocity for FV Leiden was not associated with increased risk for sepsis, an increased risk for mortality in FV Leiden carriers with sepsis was observed. Likewise, in FV Leiden carriers, the risk for urinary tract infections appeared to be decreased and the risk for skin infections to be increased.\textsuperscript{162} In a British study of 259 children with meningococcal disease, heterozygocity for FV Leiden was associated with increased risk for purpura fulminans.\textsuperscript{163} In conclusion, the factor V Leiden polymorphism appears to be associated with increased risk for coagulation disorders; nonetheless, its role in sepsis is as yet uncertain.

Thrombin-activatable fibrinolysis inhibitor (TAFI), a peptidase activated by thrombin, is a potent inhibitor of fibrinolysis. In a Dutch study involving 50 patients with meningococcal disease, a specific polymorphism of the TAFI gene was associated with increased risk for meningococcal disease mortality.\textsuperscript{164} Nonetheless, no further evidence on the role of TAFI polymorphisms in sepsis was located. Genetic polymorphisms of other constituents of the coagulation/fibrinolysis pathways may warrant investigation; nonetheless, despite their exploration in the context of thrombosis and cardiac disease (reviewed in reference 144), evidence regarding their involvement in sepsis is limited.

**Stress Hormone Polymorphisms**

Studies in populations of critically ill patients have provided evidence of the striking alterations in the hypothalamic-anterior pituitary axis hormones, and of their association with severity and mortality.\textsuperscript{165,166} Targeted endocrine interventions, including physiologic corticosteroid replacement therapy and intensive insulin therapy appear to improve survival in sepsis.\textsuperscript{167,168} Nonetheless, investigation of neuroendocrine responses in sepsis is limited. Inflammatory responses are highly integrated with neuroendocrine activation,\textsuperscript{169} and these 2 mechanisms should not be studied in isolation.

Multiple polymorphisms have been described in components of the hypothalamic-pituitary-adrenal (HPA) axis, which is fundamental for the response to the stress of sepsis.\textsuperscript{170} For example, an adrenocorticototropic hormone (ACTH) receptor promoter polymorphism appears to lead to decreased adrenal responsiveness to ACTH,\textsuperscript{171,172} which may be of essence for these individuals’ response to septic challenges. In addition, corticosteroid-related gene polymorphisms may interfere with stress and metabolic responses,\textsuperscript{173-175} and polymorphisms in genes encoding for peptides that hydrolyze cortisol may account for sustained plasma cortisol levels, interfering with cardiovascular regulation.\textsuperscript{176} Furthermore, a pro-opiomelanocortin polymorphism may associate with serum levels of leptin,\textsuperscript{177} a metabolism-regulatory peptide that is elevated in MODS and sepsis.\textsuperscript{178,179} In addition, functional polymorphisms of the growth hormone (GH) gene, a hormone central for the neuroendocrine response to sepsis,\textsuperscript{166} have been described in humans.\textsuperscript{180} At present, hormone polymorphisms have not been investigated in
relation to sepsis, despite the pivotal role of neuroendocrine responses for patient survival.

**Synthesis and Proposed Framework**
Despite obvious discrepancies and methodological limitations, taken together, these data suggest that genomic variations may have a role in shaping individual susceptibility to sepsis and/or individual risk for septic complications and death. Genomic variations may interfere with multiple aspects of recovery and cellular response mechanisms in sepsis (Figure 2).

Figure 2: Endothelial cell response as a model for the involvement of genetic polymorphisms in sepsis. Genetic polymorphisms may be involved in multiple aspects of cellular response and inflammation/recovery mechanisms in sepsis (dotted circles). a, b: pathogen recognition through transmembrane receptors; c: intracellular signaling following pathogen recognition; d: immunocyte clonal expansion and development of immune responses; e: coagulation/fibrinolysis and complement activation events; f: heat shock protein expression and cellular hibernation in response to cellular stress; g: production of pro- and anti-inflammatory cytokines; h: triggering of apoptotic cell death (immunocytes, endothelial cells); i: production of hypothalamic-pituitary stress hormones. APC indicates antigen-presenting cell; CD14, pathogen recognition accessory molecule; CTL, cytotoxic T cell; HSP, heat-shock proteins; IL, interleukin; Mφ, macrophage; NK, natural killer cell; TLR, toll-like receptor; and TNF, tumor necrosis factor.
Such evidence corroborates a long-held premise of nursing theory and practice: individualized care. Individualized care involves nursing care activities based on individual patients’ needs, and encompasses diverse dimensions, such as nursing ethics, interventions, and patient education.182 However, the concept and correlates of individualization of care may remain obscure,183 whereas, often, it has been equated to offering choice to patients and to patient autonomy.183 Nonetheless, individualized care is a much broader concept grounded on the hypothesis that patients’ responses to disease may vary according to specific individual differences, which, when properly addressed, increase chances for improved patient outcomes. Evidence originating from genetic research, for the first time, offers an extended biological foundation for the theoretical concept of individualized care. In the future, genomic variations may guide specific individualized strategies of care for patients at risk for (and/or with) sepsis based on the identification of a wide array of genetic characteristics. However, genetic research in sepsis is unlikely to produce any clinically meaningful results, if the multifactorial nature of sepsis and inflammation is not taken into account for the design of genetic association studies and of tailored clinical trials. The disappointment with the administration of antimediator therapies,184 over the past years, has fueled the argument that linear cause-effect dynamics may not apply to exceedingly multifactorial phenomena such as sepsis. Conversely, complex nonlinear systems, governed by the laws of chaos—where small perturbations in 1 variable are likely to affect all other variables and their interactions—are proposed as a new paradigm for sepsis.185,186 In such a model, the interconnections among variables, which form an expanding dynamic web of events, are more important than the variables themselves.185 Interconnections within the web amplify minor variations in such a way that system outcomes may diverge largely because of subtle differences in initial conditions (sensitive dependence on initial conditions), for example, the presence of a few allelic variations. Within this paradigm, nursing and medical care have the potential to attract the system to an outcome by inflicting targeted minor changes to initial conditions. Therefore, theoretically, knowledge of individual variations early on, before the organism takes the path of MODS and death, and targeted therapeutic adjustments may lead individual illness trajectories to desired outcomes. Nonetheless, major advances in diagnostics and therapy, new approaches to mathematical modeling, and a giant leap in the paradigm of care from linear to complex are needed before individualized care plans can address genetic variation. Microarray technology may provide a means for accurate genotyping of hundreds of SNPs, simultaneously,187,188 and a means for detecting and quantifying equally large groups of peptides in plasma.189,190 In addition, recent advances in dynamical sepsis modeling191–195 may provide the background for new multivariate modeling approaches that will fit the sepsis phenomenon better than traditional multivariate statistics. Moreover, our theoretical framework needs to be expanded from a linear flow diagram to a more naturalistic web-like representation of human responses to disease. In such frameworks, psychocognitive responses and interactions must be taken into account.196

Conclusion

Our increased awareness of the genomic variations as factors in the susceptibility to sepsis further stresses the complex multifactorial nature of the disease and calls for increased efforts to individualize and innovate care in these patients. Nonetheless, genetic association studies in sepsis exhibit methodological limitations, which need to be addressed in the future. In the future, multivariate exploration of the effect of simultaneous variations in a wide array of genes involved in sepsis may provide the basis for genetic counseling in the therapy of the critically ill. However, genetic counseling in critical illness, although partially attainable on the basis of evidence on distinct SNPs, is unlikely to be effective before microarray technology becomes available at the bedside. In addition, complex systems approaches need to be explored in order to expand the current linear theoretical representations of sepsis, which limit our ability to comprehend the pathophysiology of multiple interactions and to devise effective therapeutic approaches. For the time being, there is a lack of bedside tools to aid clinical decision making on the basis of the specific care needs of patients according to their genetic makeup. Nonetheless, experienced critical care nurses may need to remain aware of the potential genetic basis of individual patients’ responses to
acknowledgments.

In addition, critical care nursing research may need to explore the efficacy of alternate care plans according to individual genetic predisposition.

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