Clinical Infectious Diseases

BRIEF REPORT

A First Unexplained Invasive Encapsulated Bacterial Infection in Young Adults Associated With High Mortality and Readmission Rates

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We find that patients ≤40 years old with a first invasive encapsulated bacterial infection have a high likelihood of death or readmission within 23 months. It is imperative to highlight them for immunological screening and initiate prophylactic interventions and treatment.

Keywords. primary immunodeficiency; bacterial infections.

Primary immunodeficiencies (PIDs) are a complex group of diseases associated with recurrent infections. The European Society of Immunodeficiency promotes 6 warning signs for identifying immunodeficiency in adults [1]. Their guidelines state that a patient with ≥2 severe bacterial infections should be screened for PID. Although it would be assumed that the majority of PIDs are diagnosed in infancy, a review of prevalence data in 2013 estimated that only 30.6% of PID diagnoses occurred in patients <15 years old [2]. A study of 10% of the US population using 2 large medical insurance company databases estimated the prevalence of PID to be as high as 3.9–5.1 per 10 000 population [3]. The use of antibiotics and improvement in living conditions may have allowed individuals who are susceptible to infection to survive, despite not being immunocompetent [4].

A retrospective 3-center study in French hospitals [5] identified 84 patients aged 18–40 years with invasive infections by encapsulated bacteria over a period of 3 years. Of these patients, 38 had no known predisposition to infection, and PID was confirmed in 9 of the 29 who agreed to be screened, in 7 after the first-ever invasive infection and in 2 after a second episode. This study suggests that there is a "golden window" after the first invasive infection episode to diagnose PID, at a stage when prophylactic antibiotics and/or immunomodulation might be life-saving.

We retrospectively audited the notes of patients <40 years old admitted to Addenbrooke's Hospital with the 5 most common unexplained invasive bacterial infections to assess outcomes and immunological screening and determine whether we have missed opportunities of care.

METHODS

The Addenbrooke's Hospital microbiology department database was searched for any sterile samples that were positive for *Streptococcus pneumoniae*, *Streptococcus pyogenes* group A, *Neisseria meningitidis*, *Neisseria gonorrhoeae*, or *Haemophilus influenzae*. The search included cultured samples from blood, cerebrospinal fluid, and aspirates of tissue fluid from normally sterile sites. Samples from normally sterile sites positive by polymerase chain and microarrays for bacterial DNA of the same organisms were included. The search was limited to samples taken after the introduction of electronic medical records until the search date and to patients hospitalized in Addenbrooke's Hospital. These results were used to cross-reference in the electronic records software EPIC (Epic Software Corporation). Patient outcomes and immunological screening status were then assessed by reviewing electronic medical records.

Each patient's records were scrutinized for the following historical parameters: age at infection, number of previous invasive infections, and the following exclusion criteria: mixed culture organisms, aplastic anemia, autoimmune disease, current cancer, cytotoxic therapy, epithelial barrier breakdown (eg, burns), alcohol excess, graft-vs-host disease, human immunodeficiency virus infection, immunosuppressive therapy, intravenous drug use, kidney disease, liver failure, pregnancy, relevant anatomic defects, relevant surgical history type 2 diabetes, and use of oral steroids. The particular episode was then analyzed to determine whether any immunodeficiency screening was undertaken and whether the infectious diseases department was consulted. As a measure of outcome, readmission or death between the documented infective episode and the search date ("follow-up time") was used.

An adequate screen for immunodeficiency was defined as one assessing complement function (CP50, AP50, C3, and C4 levels), antibodies (total immunoglobulin [Ig] G, IgM and IgA levels, functional tests against specific antigens [serotype specific Pneumococcal antibodies, *Haemophilus influenzae* type B, Tetanus Toxin], and pneumococcal strain vaccine response in the context of *S. pneumoniae* infections), and lymphocyte systems (lymphocyte phenotype). If screening contained all the

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parameters included in the standard protocol, it was deemed adequate to diagnose or exclude a relevant immunodeficiency.

RESULTS

Data were available between 27 October 2014 and 18 January 2018 (1179 days). A total of 936 samples were generated by the search, including 863 culture samples and 73 polymerase chain samples belonging to 545 unique patients. Of these patients, 255 had been treated in Addenbrooke's Hospital so had EPIC records to scrutinize. Among these patients, there were 135 *S. pneumoniae*, 77 *S. pyogenes*, 14 *H. influenzae*, 29 *N. meningitidis,* and no *N. gonorrhoeae* cases.

Of the 255 patients, 155 were excluded because they were ≥40 years old at the time of infection (46 of whom also met exclusion criteria), 2 because they had >1 episode of infection, and 54 patients because they had 1 of the aforementioned exclusion criteria. There were no patients with congenital asplenia, and all patients who had undergone splenectomy were ≥40 years old. A summary of the exclusions and demographics of the populations can be found in Supplementary Figure 1. After applying the exclusion criteria, we identified 44 patients <40 years old with a first episode of unexplained invasive bacterial infection. The median follow-up time between the positive samples for these individuals and the search being conducted was 699 days (1.9 years).

Patients' immunological screening was assessed as outlined in Methods. A screening attempt was defined as the performance of any test included in the immunological screening panel described in Methods.

Most patients were not immunologically investigated. Thirteen of 44 had some form of screening attempt; 11 of 13 attempted screens were performed explicitly to rule out immunodeficiency, and only 1 was adequate to do this. Of the 2 remaining investigations, 1 was ordered as part of a myositis workup, and 1 was ordered from a general physician practice with no stated reason in the hospital notes.

PID was "excluded" prematurely in 7 of 13 patients after only C3, C4, IgG, IgM, and IgA levels were investigated and results came back normal. Only 1 of 13 screening attempts was adequate to exclude PID. The results of this patient's investigations proved inconclusive, leading the clinician to use the genomic test for rare immune disorders (GRID) to establish a diagnosis. The GRID result came back with no genetic matches. Another patient almost had an adequate screen that was completed outside study period and was referred for GRID testing, which is still pending. Both patients have clinical pictures consistent with PID but are still awaiting a genetic diagnosis.

A large proportion of infections were not explained at all. These infections were presumably consigned to the realms of serendipity and misfortune. Our results highlighted physicians' preference for ordering specific immunological tests in preference to others. Only 2 of 44 patients had complement function tests, with another 6 having only had C3/C4 titer measurements. Almost all immunological screening was immunoglobulin subset titers. Ten of 44 patients were seen by the infectious diseases team, including 6 of those with immunological screening. Patients were much less likely to under immunological screening if they did not encounter then infectious diseases team (screening in 7 of 34).

Figure 1 shows the number of patients who had been readmitted or died of any cause during the study period. The proportion of this cohort that had poor final outcome was large; 22.8 % were readmitted, and 7% died during the median follow-up period of 23 months. The circumstances of the readmissions and deaths were subsequently investigated. At least 9 of the 13 patients in question had readmissions or deaths that were suggestive of immunodeficiency.

The investigations in these 13 patients have not yielded a genetic or biochemical diagnosis of PID. Three patients died of an infectious cause, all between 3 and 48 hours after admission. They had no immunological investigation. Of the remaining 10 patients, only 5 had any immunological investigation. Four of the 5 had PID dismissed as a diagnosis after only C3, C4, IgG, IgM, and IgA levels were investigated and proved normal. One of these 5 was 1 of 2 patients referred for GRID, described above, despite having no immunological investigation during the first admission.

DISCUSSION

We make the important observation that 7% of all patients <40 years old who present with their first severe bacterial infection will die, and up to a quarter are readmitted within a median time of 1.9 years. Some of the readmissions and deaths seem potentially preventable by interventions like the initiation of prophylactic antibiotics. The finding of high mortality rates in patients infected with *S. pneumoniae* and *N. meningitidis* suggests the clinical need to produce an immunological screening strategy for identifying individuals at risk of PID and death.

We found that immune screening is not happening on a wide basis, with less than half of the patients having any level of screen, even in a hospital that has access to immunological expertise. In these cases, no investigation was undertaken to help determine why these patients had acquired these relatively rare, very serious infections.

Within the cohort of patients who were screened, the efficacy of investigations is low. Most screens that were undertaken were incomplete and incorrectly used to exclude immunodeficiency. The bias for antibody/lymphocyte screening over complement screening points to a need for further education for clinicians working with infections. Almost half of the patients seen were assessed by infectious diseases clinicians, providing an

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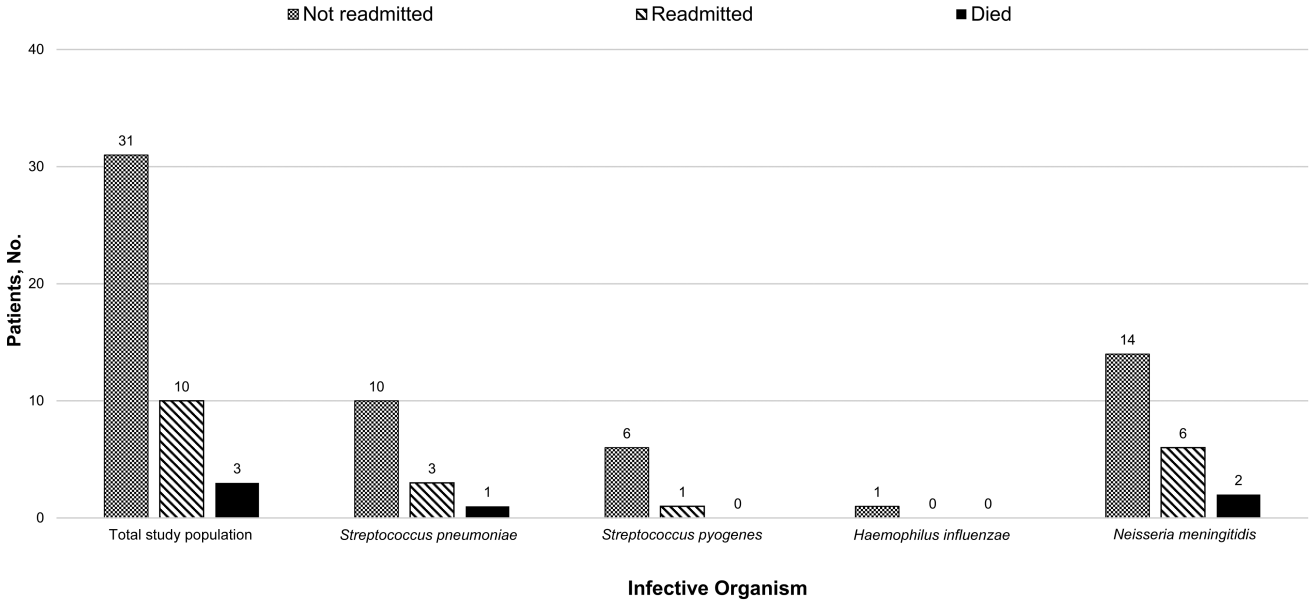

Figure 1. Readmission and death counts in patients <40 years old with unexplained invasive encapsulated bacterial infections. A total of 44 patients were observed over a median follow-up period of 699 days.

opportunity to educate the primary treating teams. Combined with the findings of Sanges et al [5] , our findings highlight the fact that young patients with first presentation of a bacterial infection represent a special group with high associated morbidity and mortality rates. There is a clinical need for further education of the physicians encountering these patients, including pediatricians, microbiologists, and infectious diseases clinicians.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Note

Potential conflicts of interest. D. K. declared the following financial support over the last 36 months: payment of expenses for a teaching day on Immunology for Infectious Diseases and Immunology Practitioners from Shire (January 2018); sponsorship to attend medical meetings from Shire and Commonwealth Serum Laboratories Behring (2018–2019); and payment of expenses and a registration fee to attend a conference on the genomics of rare diseases at Sanger Centre, Hinxton, from the Department of Biochemistry and Immunology, Addenbrooke's Hospital, charitable funds (February 2019). All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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