Hospital-acquired Pneumocystis pneumonia: a renewed concern?

Pneumocystis pneumonia (PCP), caused by the fungus Pneumocystis jirovecii, is a life-threatening pulmonary infection in immunocompromised hosts. Solid organ transplant (SOT) recipients are among those at increased risk, with infection attributed to reactivation of dormant colonisation1. Prior to the institution of routine antimicrobial prophylaxis, the overall incidence of PCP in SOT recipients was 5–15%, with the lowest incidence in kidney recipients (2–15%) and the highest, in lung and heart/lung recipients (10–40%)2,3. Prophylaxis with trimethoprim-sulfamethoxazole (TMP-SXZ) has reduced the risk of PCP by ≈91% and has largely eliminated PCP within the first year of transplantation. Prophylaxis is important since PCP-related mortality is as high as 60% despite treatment with TMP-SXZ2,4,5. Late infection was considered highly unusual1,6. However, the optimal duration of prophylaxis is uncertain. The occurrence of recent PCP case clusters in kidney transplant units in Europe and Asia (summarised in a review article; see reference 6)6 and in Australia7 has challenged our current appreciation of PCP as an ‘infection of the past’ outside patients with HIV/AIDS. It also gives pause to the likelihood of de novo infection, its mode of transmission and to the validity of current antimicrobial prophylactic regimens used, if any. This article outlines the clusters in Australia, hypothesises why this may have occurred and presents the recent consensus proposal for outbreak containment and...
prophylaxis against PCP. Details of the outbreaks in other regions are not reviewed.

In organ transplant recipients, PCP typically presents with acute breathlessness, dry cough and progressive respiratory failure with normal lung auscultation; severe infection is common. In Australia, a nosocomial cluster was recognised, beginning in 2010 at a Sydney hospital and subsequently in almost half of the kidney transplant units on the eastern seaboard over a 2-year period. In the index unit, 14 transplant recipients were affected occurring 6.3 ± 5.3 years (mean ± SD) after transplantation, well beyond the hospital’s 6-month (TMP/SXZ) prophylaxis period; this hospital experienced a second cluster following discontinuation of prophylaxis (n = 8 patients). Clusters then emerged in 10 other Sydney metropolitan and district hospitals (n = 38 patients) and seven interstate units (n = 36). In total, 95 PCP cases were identified (87 in kidney recipients, 4 in liver recipients, 1 in a liver-kidney recipient and 3 in kidney-pancreas recipients). There were 14 deaths (mortality 14.4%) and 10 additional kidney allograft losses. Epidemiological investigations with detailed contact tracing in the index and other hospitals found co-localisation of case patients to common locations including that of patients cared for, facilitated by travel of infected patients. In the index hospital, independent risk factors included previous cytomegalovirus (CMV) infection (odds ratio [OR] 65.9; P < 0.001), underlying pulmonary disease (OR 10.1, P = 0.002) and transplant dysfunction (OR 1.6; P = 0.006). These results are consistent with an earlier study where risk factors for PCP were the number and type (steroid-resistant therapeutic modalities) of rejection treatment and CMV infection.

Multilocus sequence typing (MLST) involving four loci (the internal transcribed spacer [ITS] 1 and 2 regions, mitochondrial large subunit [mtLSU], B-tubulin [B-tub] and dihydropteroate synthetase [DHPS] genes) targeting the known variable regions within the \textit{P. jirovecii} genome was undertaken to define the molecular epidemiology of the Australian outbreak. Analysis of concatenated DNA sequences from strains recovered from patients at the index hospital revealed a predominant ‘outbreak’ sequence type (ST1) with a closely related sequence type, ST2, which differed from ST1 only by a single nucleotide polymorphism in the \textit{mtLSU} region; the \textit{B-tub} and \textit{DHPS} loci yielded the least genetic variability. Both ST1 and ST2 sequence types were phylogenetically distant from the prevalent circulating \textit{P. jirovecii} genotypes in the community at the time of the outbreak. MLST allele types and sequence types are accessible online at: mlst.mycologylab.org.

In all instances, cohorting of all cases until patient death, or discharge in many cases, was undertaken as well as the institution of respiratory precautions. Ultimately the outbreaks were controlled by universal TMP-SXZ prophylaxis (for 12 months) in all potently exposed patients. Sampling of air in the corridors and rooms of one transplant unit by a solid-construct inhouse protocol (unpublished) and sampling of clinic staff by analysing oral rinses yielded no \textit{P. jirovecii} DNA.

The Australian experience indicates that patient-to-patient transmission mediated by droplet spread best explains the epidemiology of the nosocomial outbreaks, supported by individual exposure history and molecular studies; this is consistent with findings from other countries. \textit{P. jirovecii} strains of unique molecular-type strains have been recovered from infected transplant recipients, yet strains from different geographic regions have either been of identical genotype or have been distinct between regions. Most recently, Rostved et al. observed three unique genotypes among renal and liver transplant patients affected in three distinct \textit{P. jirovecii} clusters. \textit{P. jirovecii} may be recovered from air near infected patients using liquid impactor air sampling devices, although with markedly decreasing yields with increasing distance from patients; in the single Australian unit where air sampling was attempted, \textit{P. jirovecii} was not recovered from environmental air. It is highly unlikely that there was a common environmental source(s) since multiple case clusters occurred in disparate locations along the eastern seaboard of Australia. \textit{P. jirovecii} has evolved as a pathogen highly specific for humans and no environmental forms have been identified.

Studies in the index hospital were also unable to implicate transmission of infection from immunocompetent clinical staff populations. Le Gal et al. have reported molecular evidence of colonised patients as potential infectious sources of \textit{P. jirovecii}, although further evidence is required to support this hypothesis. Immunosuppressive therapy in Australia at the time of the outbreaks was relatively homogenous and had changed little over 5 years. Finally, the widespread dissemination of PCP cases and disease severity infers that the outbreak \textit{P. jirovecii} strains have increased virulence, but this hypothesis is untested.

Refocussing of attention on outbreak control approaches has led to consensus Australian recommendations by the Transplantation Society of Australia and New Zealand. These include the following recommendations: (i) transplant programs should implement immediate universal prophylaxis for all patients in the affected unit; (ii) cohorting/isolation of patients for at least 14 days after initiating PCP treatment; (iii) genotype examination; and (iv) minimum duration of antimicrobial prophylaxis following \textit{de novo} transplant: kidney, 6–12 months; liver, 3 months, heart, 12 months; and lung, indefinitely.

In conclusion, with TMP-SXZ prophylaxis, the epidemiology of PCP in modern organ transplantation indicates that infection now presents late after transplantation, increasingly within clusters within hospitals, and displays identical genotypes. Hence most infection can represent a public health problem. Genotyping of all isolates using standardised methods to identify related clusters and mandatory reporting to allow preventative measures are worthy of consideration.

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References

20. Cushion, M. (2010) Are members of the fungal genus Pneumocystis (a) commensals, (b) opportunists, (c) pathogens, or (d) all of the above? PLoS Pathog. 6, e1001009. doi:10.1371/journal.ppat.1001009

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