



Figure 3. Revised view of the development of transplant arteriosclerosis after solid-organ transplantation (see next page for legend) (fig003jhg).

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The development of transplant arteriosclerosis (TA) and subsequent chronic transplant dysfunction (CTD) can be divided in five different phases. (a) Phase 1. Soon after transplantation (days to weeks), the vascular wall is infiltrated with inflammatory cells as a result of host alloreactivity directed against the graft. This inflammatory response is characterised by perivasculitis (adventitial inflammation) and attack of graft endothelium by recipient inflammatory cells (endothelialitis). (b) Phase 2. The alloreactive response leads to destruction of the endothelial cell (EC) lining of the graft, resulting in EC denudation of the luminal surface of the vascular wall. Concomitantly with the disappearance of the EC lining, medial vascular smooth muscle (VSM) cells start to disappear as a result of apoptosis due to the ongoing inflammation in the adventitia. Complete absence of the medial VSM cells is observed, with only the elastin scaffold remaining. (c) Phase 3. Rebuilding of the damaged vessel wall, which has lost appropriate function, starts: a new EC layer of recipient origin (re-endothelialisation) is built both by ingrowth of recipient ECs over the denuded intima starting at the side of anastomosis as well as by recruitment of circulating ECs, which may originate from a non-bone marrow source (such as the host vascular wall). (d) Phase 4. VSM cell replacement starts either through ingrowth of recipient VSM cells into the graft intimal space starting at the side of the anastomosis, or from circulating, non-bone marrow derived, recipient VSM (progenitor) cells. (e) Phase 5. Initial appearance of VSM cells is followed by intimal hyperplasia caused by uncontrolled proliferation of VSM cells, resulting in luminal occlusion (TA) and eventually CTD (**fig003jhg**).