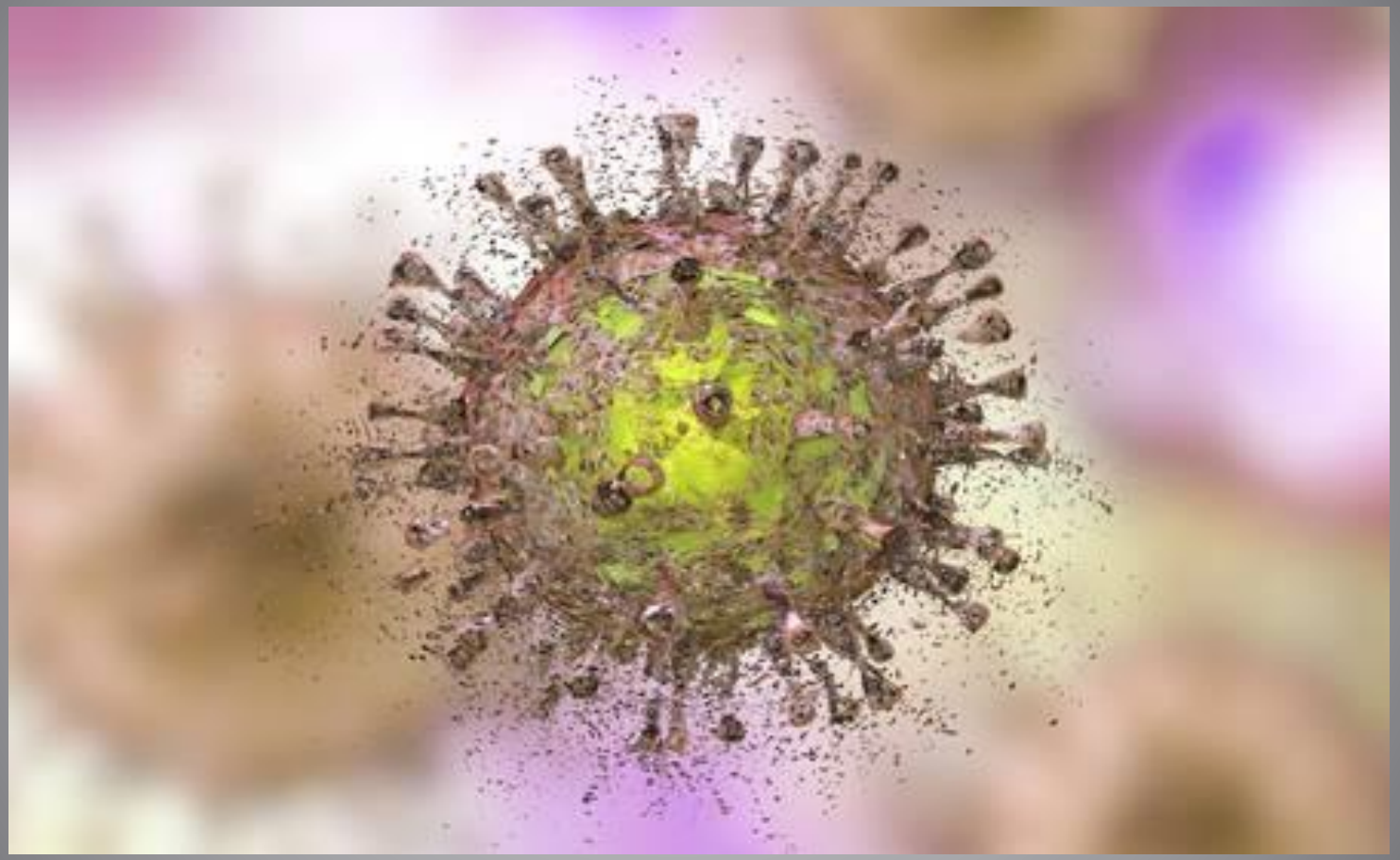
CMV CLINICAL



Dr Adele Melton
Gastroenterologist
MBChB (Otago), FRACP

Overview

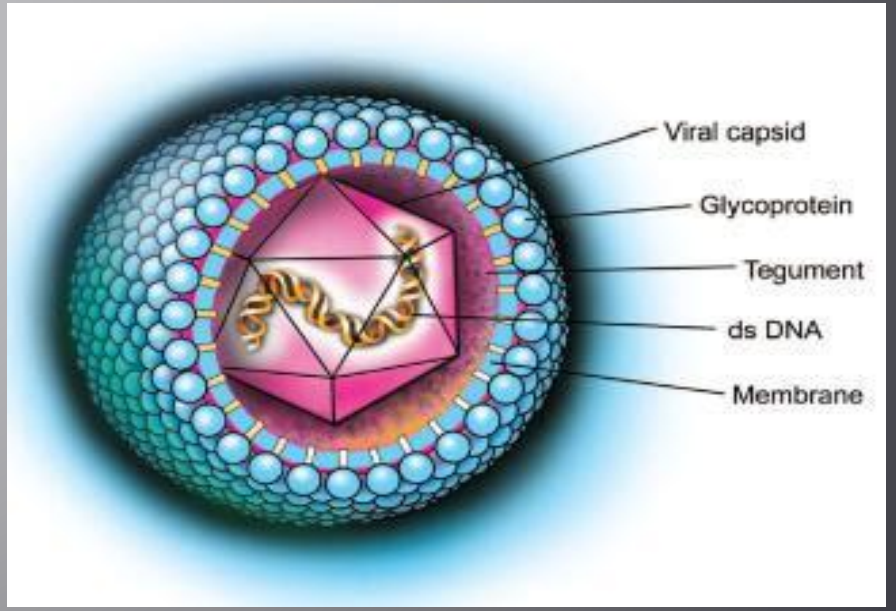
(1) Case presentation – CMV in IBD

(2) Prevalence

(3) Treatment

(4) Recommendations / Guidelines

(5) Questions

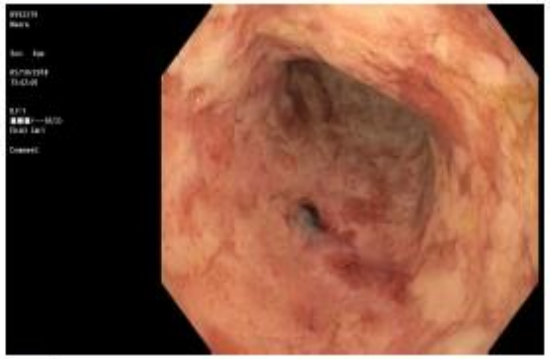


Case presentation

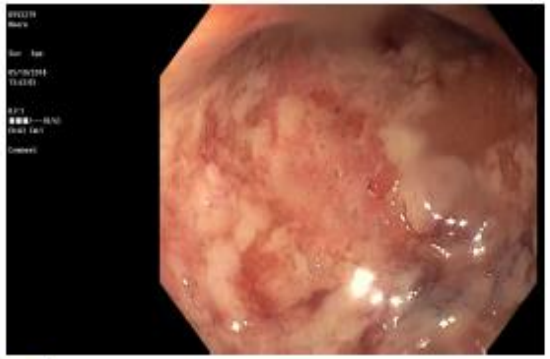
- 60 year old male

- Background:
  - UC, pancolitis (April 2018)
    - on Azathioprine and Pentasa
  - AVR (May 2017)
    – for Enterococcus faecalis endocarditis and severe AR
  - MSSA aortic valve endocarditis (Nov 2016)
    – complicated by sepsis, discitis, osteomyelitis, septic arthritis
  - Chronic hepatitis C, genotype 1b
    – Fibroscan: 5.4kPa, minimal fibrosis
  - Previous IVDU
  - Chronic pain
  - Ex-smoker
  - Anxiety / Depression

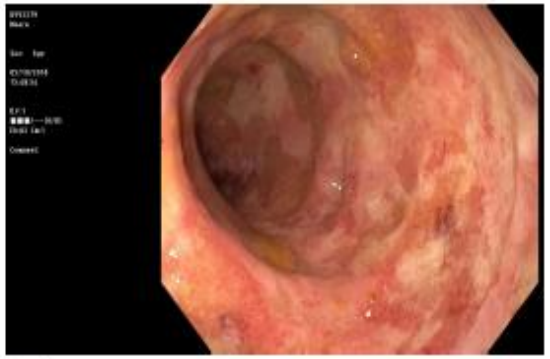
Images:



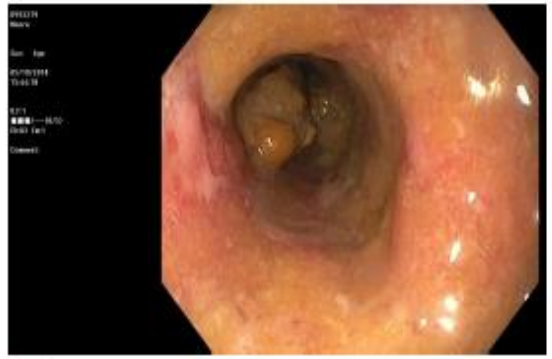
2 Rectum



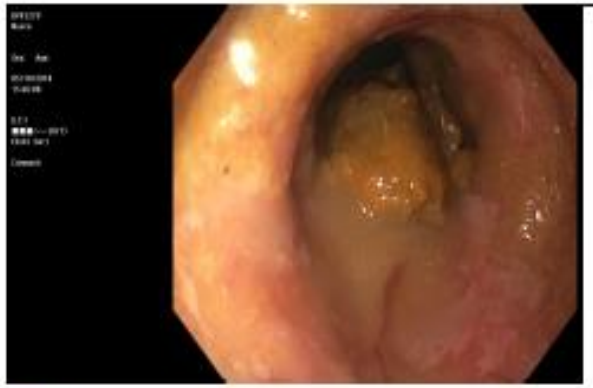
3 Sigmoid Colon



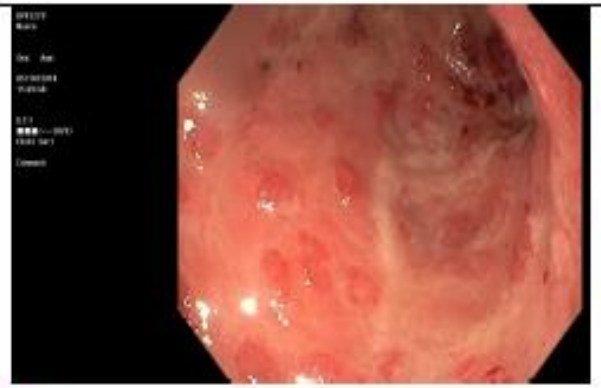
4 Sigmoid Colon



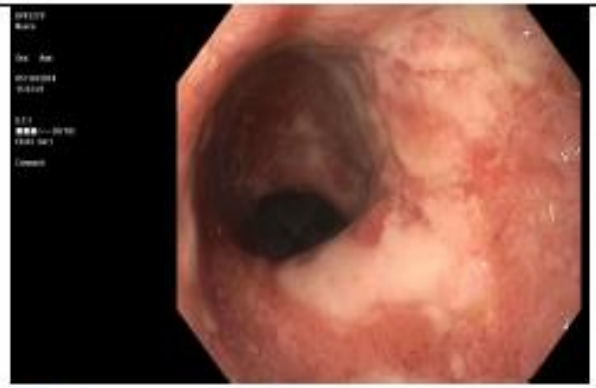
5 Descending Colon



6 Descending Colon



7 Sigmoid Colon



8 Sigmoid Colon

COMMENTS:
The features are of severe chronic proctocolitis with severe activity (including widespread ulceration), and scattered CMV viral inclusions. CMV DNA was also detected by PCR in the tissue sampled from all three sites. The overall appearances would be consistent with known ulcerative colitis with superimposed CMV-associated proctocolitis.

DIAGNOSIS
1-3) DESCENDING COLON, SIGMOID COLON AND RECTAL BIOPSIES:
- SEVERE CHRONIC PROCTOCOLITIS WITH SEVERE ACTIVITY
- CMV VIRAL INCLUSIONS PRESENT

CMV IgM	Negative
CMV IgG	732.0 (Positive) UA/mL

CMV Specimen type			
CMV Viral load	<137		IU/mL
CMV Viral load	<2.18		log IU/mL
Cytomegalovirus PCR comment			

CMV Specimen type

Specimen type Plasma

CMV Viral load

Note: CMV viral load is now reported in international units.
Conversion factor is 1 viral copy = 0.91 IU

Cytomegalovirus PCR comment

Comments :
Viral load positive but at a very low level, below the linear range of the assay. This may affect the reproducibility of the result.

Epidemiology

- Worldwide seroprevalence 40-100%
- Highest – Asia, South America, Africa (cf. Western Europe, USA)

- Local data – National serosurvey 200,
  estimated 57% Australians aged 1-59 years seropositive

- Primary CMV infection
  → asymptomatic, mild mononucleosis-like syndrome
- Latency phase
- Reactivation → systemic immunosupression

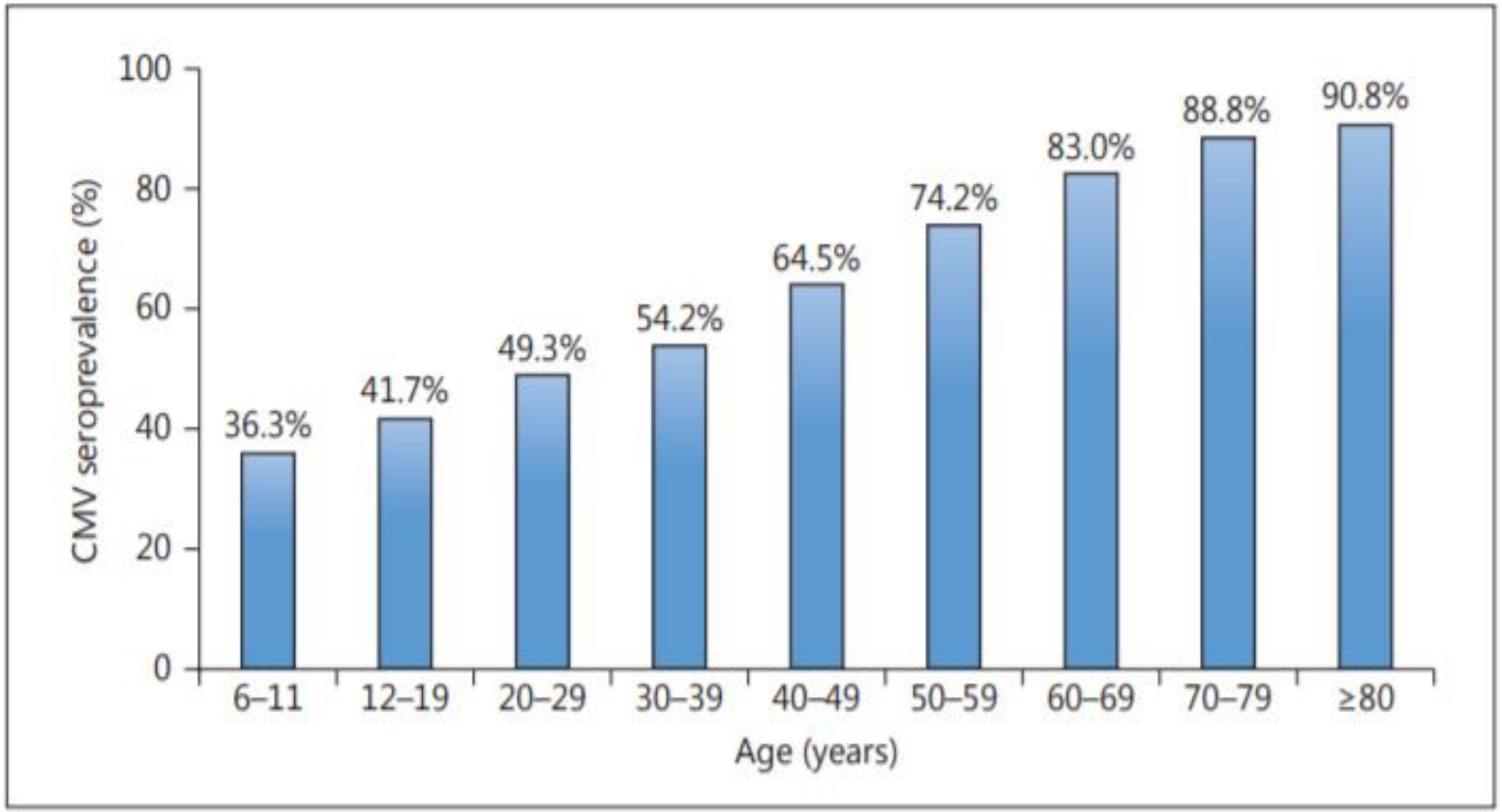


Fig. 1. Age-adjusted CMV seroprevalence in the noninstitutionalized, civilian population of the US (n = 21,639) published in the third National Health and Nutrition Examination Survey (1988–1994) [78].

Prevalence in IBD patients

- Not entirely clear
- Influenced by:
  - Selection bias
  - Small study sizes
  - Different tests - with different sensitivities and specificities
  - Geographic variation of CMV prevalence in the population

- UC >> Crohn's disease
- Moderate to severe UC; 16%-34% *

* *Kishore J, Ghoshal U, Ghoshal UC, et al. Infection with cytomegalovirus in patients with inflammatory bowel disease: prevalence, clinical significance and outcome. J Med Microbiol 2004;53(Pt 11):1155-1160.*

**Wada Y, Matsui T, Matake H, et al. Intractable ulcerative colitis caused by cytomegalovirus infection: a prospective study on prevalence, diagnosis, and treatment. Dis Colon Rectum 2003;46(10 Suppl):S59-S65.*

- Steroid-refractory UC is strongly associated with CMV

- Case-control study *
  Ratio of CMV + (by IHC) in surgical specimens of
  steroid refractory UC vs non-refractory UC
  25% **2.5%**

** *Criscuoli V, Casa A, Orlando A, et al: Severe acute colitis associated with CMV: a prevalence study. Dig Liver Dis; 2004;36:818-820*

Longitudinal Incidence and Impact of CMV Infection on IBD Hospitalizations

	Ulcerative Colitis			Crohn's Disease		
	CMV+	95% CI	p-value	CMV+	95% CI	p-value
Death (aOR)	2.81	1.56 – 5.06	<0.001	4.47	1.77 – 11.33	0.002
Colectomy (aOR)	1.03	0.79 – 1.35	0.816	-	-	-
Bowel Surgery (aOR)	-	-	-	0.68	0.45 – 1.02	0.065
Malnutrition (aOR)	3.02	2.41 – 3.78	<0.001	2.80	2.01 – 3.91	<0.001
Anemia (aOR)	1.67	1.38 – 2.01	<0.001	2.10	1.56 – 2.84	<0.001
Renal Failure (aOR)	1.79	1.23 – 2.61	0.002	2.17	1.26 – 3.74	0.005
Length of Stay (additional days)	6.93	5.73 – 8.13	<0.001	8.44	6.36 – 10.53	<0.001
Total Charges (additional dollars)	$51.704	$39,790 – $63,618	<0.001	$51,916	$34,869 – $68,963	<0.001

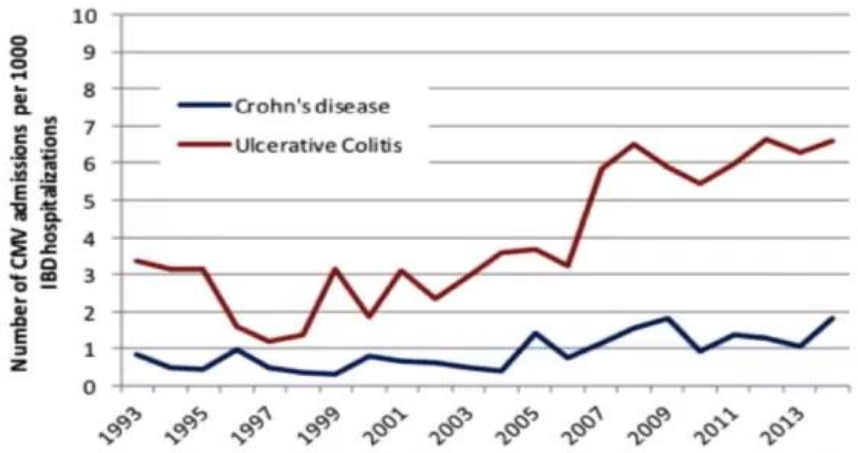
LOS, length of stay; IBD, Inflammatory Bowel Disease

Methods

- National Inpatient Sample analyzed from 1993-2014 using ICD-9 CM codes for Crohn's disease (CD), ulcerative colitis (UC), and cytomegalovirus (CMV) colitis

Results/ Conclusions

- IBD hospitalizations with CMV are rising, especially in UC
- Independent associations (table)



Hendler S, et al. Presented at DDW. June 2018. Abstract Sa1807.

However . . .

- Debate is still open if detection of CMV in severe colitis

  ? Bystander re-activation

  ? Driving / Aggravating inflammation

Mouse Model

- Nakase et al. – experimental IBD mouse model
- Mouse CMV shares high sequence homology with human CMV
- T-cell receptor (TCR)-α Knockout (KO) mouse develops spontaneous bowel inflammation similar to UC
- MCMV-infected TCR-α KO mice developed more severe colitis than non-infected mice

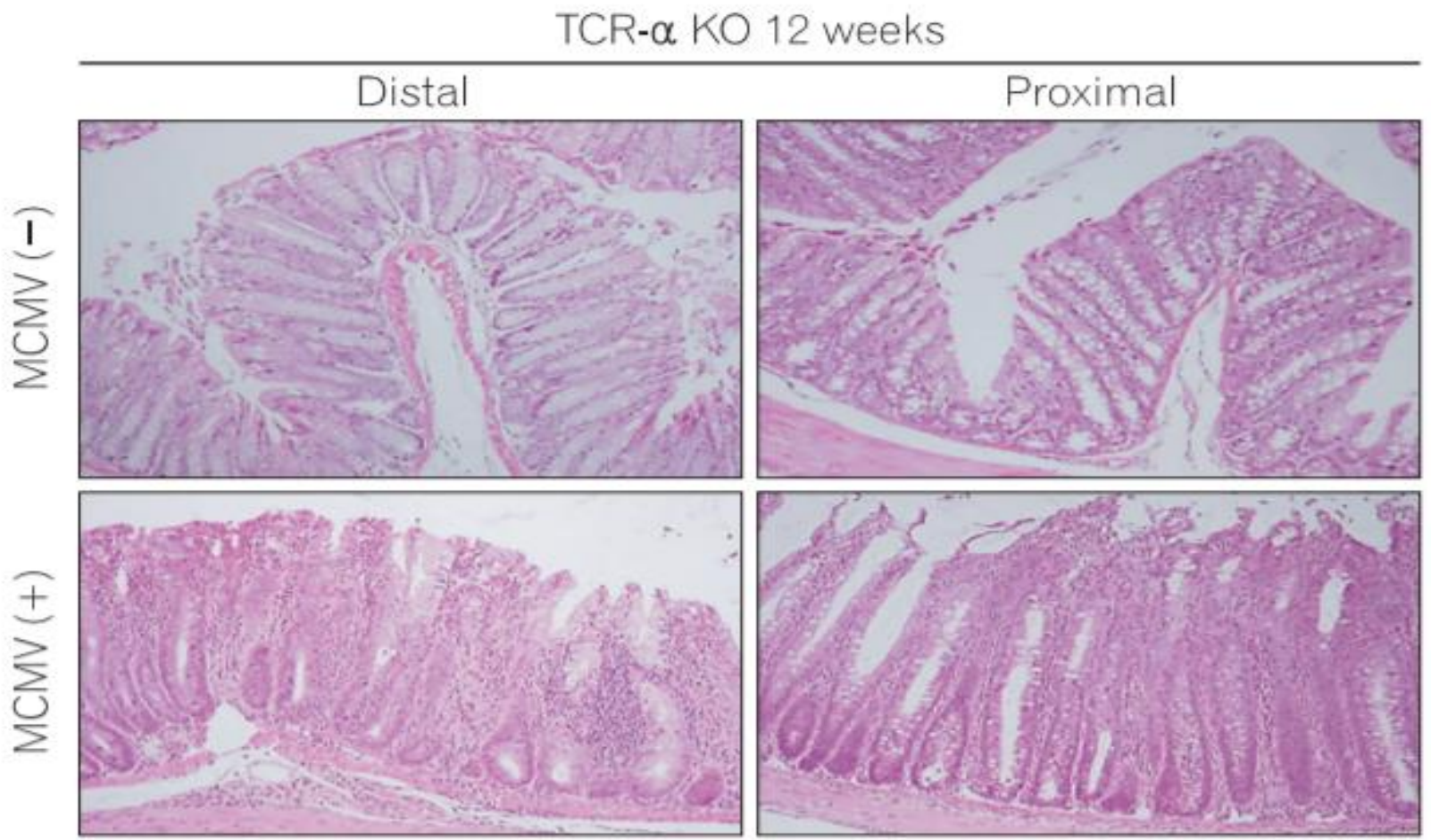


Fig. 2. Histologic findings in the proximal and distal colon in T cell receptor (TCR)-α knockout (KO) mice with and without mouse cytomegalovirus (MCMV) infection at 12 weeks. In comparison with uninfected KO mice, histological examination revealed severe hyperplasia of the epithelial cells, infiltration of inflammatory cells, and crypt loss in infected TCR-α KO mice at 12 weeks (H&E, ×200).

Treatment

- Systemic therapy
  - Ganciclovir, Valganciclovir, Foscarnet, Cidofovir

- Side effects – first-line therapy
  - Neutropenia
  - Headaches
  - Deranged LFTs
  - Rash
  - Somnolence
  - Psychosis

Future options

- Granulocyte and monocyte adsorptive apheresis (GMAA)
- Biological therapy for UC that selectively removes granulocytes/macrophages that produce inflammatory cytokines, without removing lymphocytes

- Yoshino et al.
  - GMAA did not affect CMV reactivation in UC patients with latent CMV
- Fukuchi et al.
  - CMV DNA in colonic mucosa became –ve in all UC patients +ve for CMV, who achieved remission after GMAA

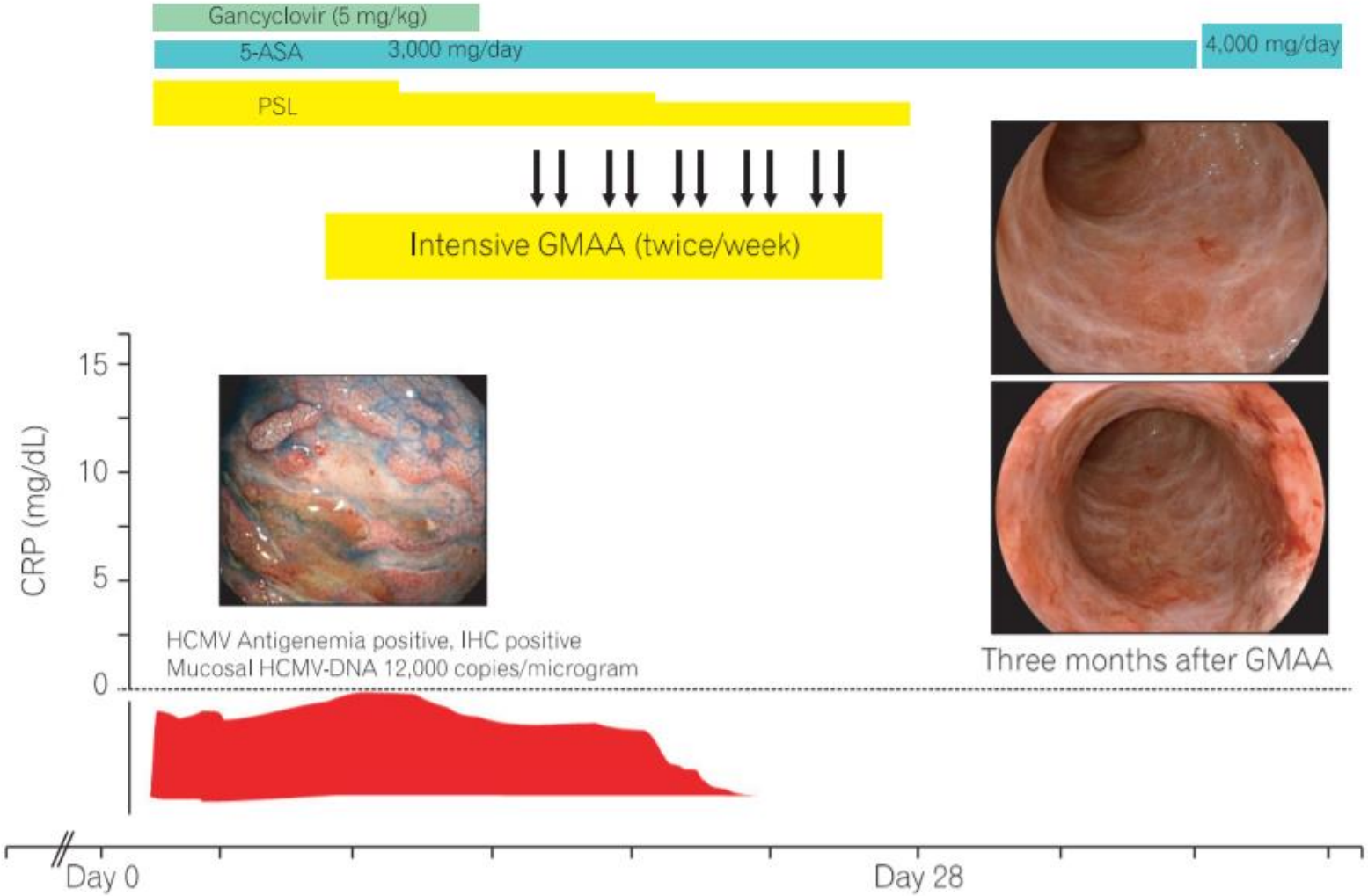


Fig. 1. Effect of granulocyte and monocyte adsorptive apheresis (GMAA) on UC patient with concomitant human cytomegalovirus (HCMV) infection. Cases of steroid-resistant UC patients with concomitant HCMV infection who were successfully treated with GMAA. Forty-nine female patients with UC, who were refractory to 60 mg of prednisolone (PSL), were transferred to our hospital. HCMV antigenemia, immunohistochemistry (IHC), and HCMV-DNA in the colonic mucosa were observed. After starting gancyclovir (5 mg/kg), abdominal symptoms such as hematochezia and abdominal pain did not subside. We initiated intensive GMAA (twice/week). After 10 applications of GMAA, the abdominal symptoms disappeared and PSL could be completely tapered. Sigmoidoscopy 3 months after initiation of GMAA showed the disappearance of the ulcerative lesions and scar formation. 5-ASA, 5-aminosalicylic acid.

Outcomes

- ? Colectomy rate
- ? Death
- ? Length of hospital stay / ICU admission
- ? Clearance / Reduction of CMV from colonic tissue
- ? Endoscopic / Histologic remission
- ? Steroid-free remission
- ? Need for escalation of medical therapy

- ? Long-term outcomes

- Kim et al. (Gut and Liver, 2014)
  - Retrospective multicentre study
  - 72 patients, mod-severe UC, CMV re-activation at the time of their initial flare
  - Mean follow-up 43.16+/-19.78 months
  - CMV positive – poor outcomes long-term
  - Ganciclovir – short-term efficacy, marginal long-term efficacy

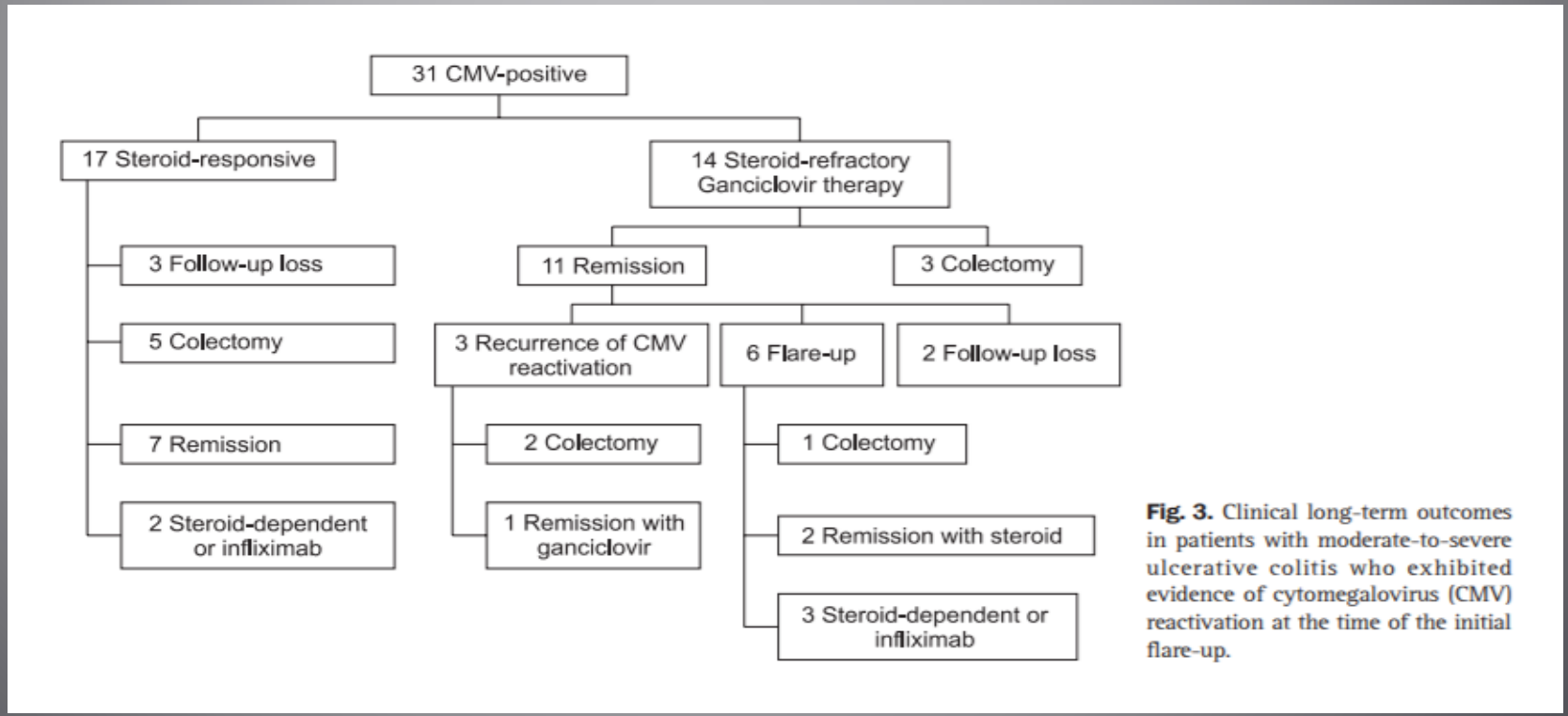


Fig. 3. Clinical long-term outcomes in patients with moderate-to-severe ulcerative colitis who exhibited evidence of cytomegalovirus (CMV) reactivation at the time of the initial flare-up.

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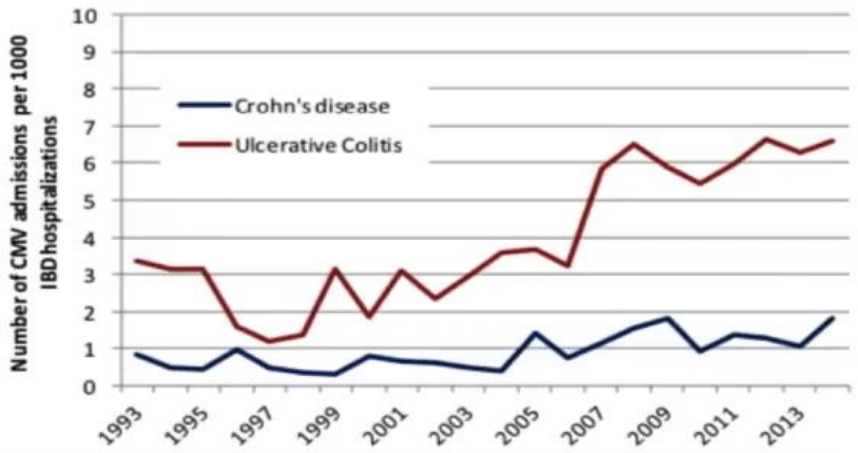

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- Hendler et al. (2018)
  - ICD-9 codes, IBD, CMV infection → linear and logistic regression
  - Estimate effect on – malnutrition, anaemia, renal failure, bowel resection, $
  - Hospitalisations 1993-2014

UC	CD	
692,694	1,274,372	Hospitalisations
1,810	616	CMV infections

  - CMV associated with higher rates of malnutrition, anaemia, inpatient mortality, length of stay, total cost
  - Increased colectomies in UC
  - Higher rates of renal failure in CD

Guidelines / Recommendations

- American College of Gastroenterology (ACG) and European Crohn's and Colitis Organization (ECCO) recommend:
  - treatment of CMV with anti-virals only when a patient with severe colitis is failing to respond to immunosuppressive therapy

- Roblin et al.
  - CMV DNA load >250 copies/mg in tissue was predictive of resistance to steroids and 2x immunosuppressives, therefore postulating that it might be prudent to treat those patients found to have high CMV DNA levels before they deteriorate

Questions